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(54) Title: 6H-THIENO<sup>2</sup>, 3-B<sup>1</sup>PYRROLE DERIVATIVES AS ANTAGONISTS OF GONADOTROPIN RELEASING HORMONE (GNRH)

(57) Abstract: The invention relates to a group of novel thieno-pyrrole compounds of Formula (I): wherein: R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are as defined in the specification, which are useful as gonadotrophin releasing hormone antagonists. The invention also relates to pharmaceutical formulations of said compounds, methods of treatment using said compounds and to processes for the preparation of said compounds.



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6H-THIENO[2,3-B]PYRROLE DERIVATIVES AS ANTAGONISTS OF GONADOTROPIN  
RELEASING HORMONE (GnRH)

The present invention relates to compounds which are antagonists of gonadotropin releasing hormone (GnRH) activity. The invention also relates to pharmaceutical formulations, the use of a compound of the present invention in the manufacture of a medicament, a method of therapeutic treatment using such a compound and processes for producing the compounds.

Gonadotropin releasing hormone (GnRH) is a decapeptide that is secreted by the hypothalamus into the hypophyseal portal circulation in response to neural and/or chemical stimuli, causing the biosynthesis and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary. GnRH is also known by other names, including gonadoliberin, LH releasing hormone (LHRH), FSH releasing hormone (FSH RH) and LH/FSH releasing factor (LH/FSH RF).

GnRH plays an important role in regulating the action of LH and FSH (by regulation of their levels), and thus has a role in regulating the levels of gonadal steroids in both sexes, including the sex hormones progesterone, oestrogens and androgens. More discussion of GnRH can be found in WO 98/5519 and WO 97/14697, the disclosures of which are incorporated herein by reference.

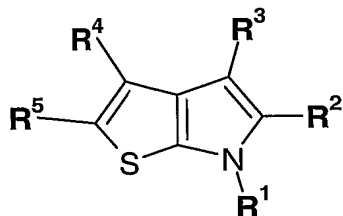
It is believed that several diseases would benefit from the regulation of GnRH activity, in particular by antagonising such activity. These include sex hormone related conditions such as sex hormone dependent cancer, benign prostatic hypertrophy and myoma of the uterus. Examples of sex hormone dependent cancers are prostatic cancer, uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The following disclose compounds purported to act as GnRH antagonists:

WO 97/21435, WO 97/21703, WO 97/21704, WO 97/21707, WO 55116, WO 98/55119, WO 98/55123, WO 98/55470, WO 98/55479, WO 99/21553, WO 99/21557, WO 99/41251, WO 99/41252, WO 00/04013, WO 00/69433, WO 99/51231, WO 99/51232, WO 99/51233, WO 99/51234, WO 99/51595, WO 99/51596, WO 00/53178, WO 00/53180, WO 00/53179, WO 00/53181, WO 00/53185, WO 00/53602, WO 02/066477, WO 02/066478, WO 02/06645 and WO 02/092565.

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It would be desirable to provide further compounds, such compounds being GnRH antagonists. Thus, according to the first aspect of the invention there is provided a compound of Formula (I),

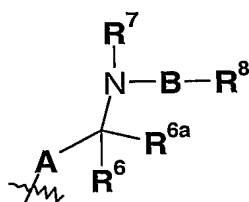


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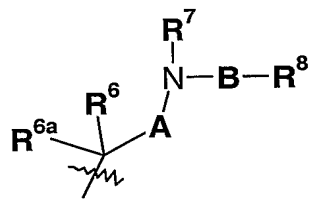
Formula (I)

wherein:

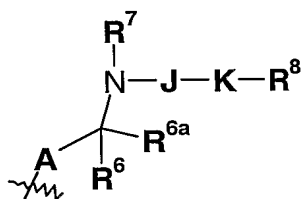
- R¹** is selected from: hydrogen, optionally-substituted C<sub>1-6</sub>alkyl, optionally substituted C<sub>1-6</sub>alkanoyl, optionally substituted aryl or optionally-substituted arylC<sub>1-6</sub>alkyl;  
**R²** is an optionally-substituted mono or bi-cyclic aromatic ring;  
**R³** is selected from a group of Formula (IIa) to Formula (IIf):



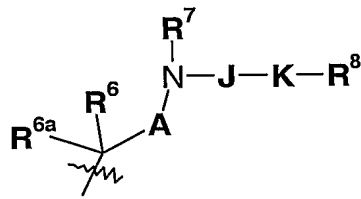
Formula (IIa)



Formula (IIb)

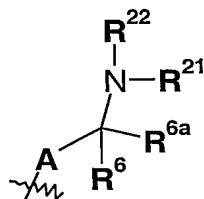


Formula (IIc)

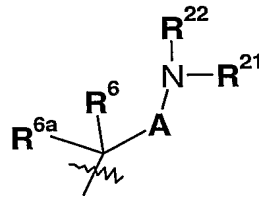


Formula (IId)

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Formula (IIe)



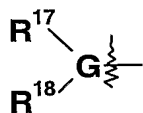
Formula (IIf)

- R⁴** is selected from: hydrogen, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted aryl, C<sub>1-3</sub>perfluoroalkyl, cyano, nitro, halo, **R⁹**O(CH<sub>2</sub>)<sub>m</sub>⁻, **R⁹**C(O)N(**R¹⁰**)(CH<sub>2</sub>)<sub>m</sub>⁻, **R⁹R¹⁰**NC(O)N(**R¹⁰**)(CH<sub>2</sub>)<sub>m</sub>⁻, **R⁹**S(O<sub>n</sub>)(CH<sub>2</sub>)<sub>m</sub>⁻ or **R⁹R¹⁰**NC(O)-(CR<sup>⁹</sup>R<sup>¹⁰</sup>)<sub>t</sub>(CH<sub>2</sub>)<sub>m</sub>⁻;

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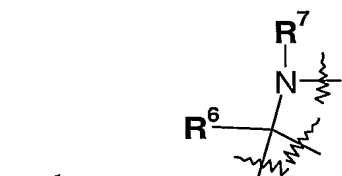
$R^5$  is a group of Formula (III):



Formula (III)

- $R^6$  and  $R^{6a}$  are independently selected from hydrogen, fluoro, optionally substituted  $C_{1-6}$ alkyl, optionally-substituted aryl or optionally substituted aryl $C_{1-6}$ alkyl, or  $R^6$  and  $R^{6a}$  taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms, or  $R^6$  and  $R^{6a}$  taken together and the carbon atom to which they are attached form a carbonyl group;

- or when A is not a direct bond the group forms a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms;



or the group forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

- $R^7$  is selected from: hydrogen, optionally-substituted  $C_{1-6}$ alkyl, optionally-substituted aryl $C_{1-6}$ alkyl, optionally-substituted aryl, optionally substituted heterocyclyl, optionally substituted heterocyclyl $C_{1-6}$ alkyl,  $R^9OC_{1-6}$ alkyl-,  $R^9R^{10}NC_{1-6}$ alkyl-,  $R^9R^{10}NC(O)C_{1-6}$ alkyl,  $-C(NR^9R^{10})=NH$ ;

or when  $R^3$  is a group of Formula (IIc) or (IId)  $R^7$  can also be of the formula  $-J-K-R^8$ ;

$R^8$  is selected from:

- (i) hydrogen,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl, halo $C_{1-6}$ alkyl,  $C_{1-4}$ alkoxy $C_{1-4}$ alkyl, hydroxy, hydroxy $C_{1-6}$ alkyl, cyano, N- $C_{1-4}$ alkylamino, N,N-di- $C_{1-4}$ alkylamino,  $C_{1-6}$ alkyl-S( $O_n$ )-,  $-O-R^b$ ,  $-NR^bR^c$ ,  $-C(O)-R^b$ ,  $-C(O)O-R^b$ ,  $-CONR^bR^c$ ,  $NH-C(O)-R^b$  or  $-S(O_n)NR^bR^c$ , where  $R^b$  and  $R^c$  are independently selected from hydrogen and  $C_{1-4}$ alkyl optionally substituted with hydroxy, amino, N- $C_{1-4}$ alkylamino, N,N-di- $C_{1-4}$ alkylamino,  $HO-C_{2-4}$ alkyl-NH- or  $HO-C_{2-4}$ alkyl-N( $C_{1-4}$ alkyl)-;
- (ii) nitro when B is a group of Formula (IV) and X is CH and p is 0;

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- (iii) C<sub>3-7</sub>cycloalkyl, aryl or arylC<sub>1-6</sub>alkyl each of which is optionally substituted by **R**<sup>12</sup>, **R**<sup>13</sup> and **R**<sup>14</sup>;
- (iv) -(**Q**)-aryl, -(**Q**)-heterocyclyl, -aryl-(**Q**)-aryl, each of which is optionally substituted by **R**<sup>12</sup>, **R**<sup>13</sup> and **R**<sup>14</sup>
- 5 wherein -(**Q**)- is selected from **E**, **F** or a direct bond;
- (v) heterocyclyl or heterocyclylC<sub>1-6</sub>alkyl each of which is optionally substituted by up to 4 substituents independently selected from **R**<sup>12</sup>, **R**<sup>13</sup> and **R**<sup>14</sup>;
- (vi) a group selected from **R**<sup>12</sup>, **R**<sup>13</sup> and **R**<sup>14</sup>;
- R**<sup>9</sup> and **R**<sup>10</sup> are independently selected from: hydrogen, hydroxy, optionally substituted
- 10 C<sub>1-6</sub>alkyl, optionally substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl, an optionally substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclylC<sub>1-6</sub>alkyl or **R**<sup>9</sup> and **R**<sup>10</sup> taken together can form an optionally substituted ring of 3-9 atoms or **R**<sup>9</sup> and **R**<sup>10</sup> taken together with the carbon atom to which they are attached form a carbonyl group;
- 15 **R**<sup>11</sup> is selected from: hydrogen, optionally substituted C<sub>1-6</sub>alkyl, or N(**R**<sup>9</sup>**R**<sup>10</sup>);
- R**<sup>12</sup> is selected from: hydrogen, hydroxy, **R**<sup>17</sup>**R**<sup>18</sup>N(CH<sub>2</sub>)<sub>cc</sub>-, **R**<sup>17</sup>**R**<sup>18</sup>NC(O)(CH<sub>2</sub>)<sub>cc</sub>-, optionally substituted C<sub>1-6</sub>alkyl- C(O)N(**R**<sup>9</sup>)(CH<sub>2</sub>)<sub>cc</sub>-, **R**<sup>17</sup>**R**<sup>18</sup>NC(O)N(**R**<sup>9</sup>)(CH<sub>2</sub>)<sub>cc</sub>-, **R**<sup>17</sup>**R**<sup>18</sup>NC(O)O(CH<sub>2</sub>)<sub>cc</sub>-, optionally substituted C<sub>1-6</sub>alkyl-OC(O)N(**R**<sup>9</sup>)(CH<sub>2</sub>)<sub>cc</sub>-, optionally substituted C<sub>1-6</sub>alkyl-SO<sub>2</sub>N(**R**<sup>9</sup>)-, optionally substituted aryl-SO<sub>2</sub>N(**R**<sup>9</sup>)-,
- 20 C<sub>1-3</sub>perfluoroalkyl-SO<sub>2</sub>N(**R**<sup>9</sup>)-; optionally substituted C<sub>1-6</sub>alkyl-N(**R**<sup>9</sup>)SO<sub>2</sub>-, optionally substituted aryl-N(**R**<sup>9</sup>)SO<sub>2</sub>-, C<sub>1-3</sub>perfluoroalkyl-N(**R**<sup>9</sup>)SO<sub>2</sub>- optionally substituted C<sub>1-6</sub>alkanoyl-N(**R**<sup>9</sup>)SO<sub>2</sub>-, optionally substituted aryl-C(O)N(**R**<sup>9</sup>)SO<sub>2</sub>-, optionally substituted C<sub>1-6</sub>alkyl-S(O<sub>n</sub>) -, optionally substituted aryl-S(O<sub>n</sub>) -, C<sub>1-3</sub>perfluoroalkyl-, C<sub>1-3</sub>perfluoroalkoxy, optionally substituted C<sub>1-6</sub>alkoxy, carboxy, halo, nitro or cyano;
- 25 **R**<sup>13</sup> and **R**<sup>14</sup> are independently selected from: hydrogen, hydroxy, oxo, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted C<sub>1-6</sub>alkanoyl, optionally substituted C<sub>2-6</sub>alkenyl, cyano, nitro, C<sub>1-3</sub>perfluoroalkyl-, C<sub>1-3</sub>perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl, **R**<sup>9</sup>O(CH<sub>2</sub>)<sub>s</sub>-, **R**<sup>9</sup>(O)O(CH<sub>2</sub>)<sub>s</sub>-, **R**<sup>9</sup>OC(O)(CH<sub>2</sub>)<sub>s</sub>-, **R**<sup>16</sup>S(O<sub>n</sub>)(CH<sub>2</sub>)<sub>s</sub>-, **R**<sup>9</sup>**R**<sup>10</sup>NC(O)(CH<sub>2</sub>)<sub>s</sub>- or halo;
- 30 **R**<sup>15</sup> is selected from: hydrogen, optionally substituted C<sub>1-6</sub>alkyl, **R**<sup>19</sup>OC(O)-, **R**<sup>9</sup>**R**<sup>10</sup>NC(O)-, **R**<sup>9</sup>C(O)-, **R**<sup>9</sup>S(O<sub>n</sub>)-;
- R**<sup>16</sup> is selected from: hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-3</sub>perfluoroalkyl or optionally-substituted aryl;

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$R^{17}$  is independently selected from: hydrogen, hydroxy, cyano or optionally substituted  $C_{1-6}$ alkyl;

$R^{18}$  is a group of formula  $R^{18a}-C(R^9R^{10})_{0-1}-$  wherein  $R^{18a}$  is selected from:  $R^{19}OC(O)-$ ,  $R^9R^{10}NC(O)-$ ,  $R^9R^{10}N-$ ,  $R^9C(O)-$ ,  $R^9C(O)N(R^{10})-$ ,  $R^9R^{10}NC(O)-$ ,  $R^9R^{10}NC(O)N(R^{10})-$ ,  $R^9SO_2N(R^{10})-$ ,  $R^9R^{10}NSO_2N(R^{10})-$ ,  $R^9C(O)O-$ ,  $R^9OC(O)-$ ,  $R^9R^{10}NC(O)O-$ ,  $R^9O-$ ,  $R^9S(O_n)-$ ,  $R^9R^{10}NS(O_n)-$ , hydrogen, optionally substituted  $C_{1-6}$ alkyl, optionally substituted heterocyclyl;

or  $R^{17}$  and  $R^{18}$  when taken together form an optionally substituted carbocyclic ring of 3-7 atoms or optionally substituted heterocyclyl;

$R^{19}$  is selected from: hydrogen, optionally substituted  $C_{1-6}$ alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$ alkyl, optionally substituted  $C_{3-7}$ cycloalkyl, optionally substituted heterocyclyl or optionally substituted heterocyclyl $C_{1-6}$ alkyl;

$R^{20}$  is selected from  $R^{12}$  or  $R^{13}$ ;

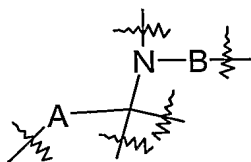
$R^{21}$  and  $R^{22}$  are independently selected from hydrogen, optionally substituted  $C_{1-6}$ alkyl, optionally substituted  $C_{3-7}$ cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl $C_{1-6}$ alkyl, optionally substituted  $C_{3-6}$ alkenyl, optionally substituted  $C_{3-6}$ alkynyl,  $-(C_{1-5}alkyl)_{aa}-S(O_n)-(C_{1-5}alkyl)_{bb}-$ ;  $R^9R^{10}NC_{2-6}alkyl$ ,  $R^9OC_{2-6}alkyl$  or  $R^9R^{10}NC(O)C_{2-6}alkyl$ , with the proviso that  $R^9$  and  $R^{10}$  independently or taken together are not optionally substituted aryl or optionally substituted aryl $C_{1-6}$ alkyl; or


$R^{21}$  and  $R^{22}$  taken together form an optionally substituted non-aromatic heterocyclic ring;

A is selected from:

- (i) a direct bond;
- (ii) optionally-substituted  $C_{1-5}$ alkylene wherein the optional substituents are independently selected from: optionally-substituted  $C_{1-6}$ alkyl, optionally-substituted aryl or optionally substituted aryl $C_{1-6}$ alkyl;
- (iii) a carbocyclic ring of 3-7 atoms;
- (iv) a carbonyl group or  $-C(O)-C(R^dR^d)-$ , wherein  $R^d$  is independently selected from hydrogen and  $C_{1-2}$ alkyl;

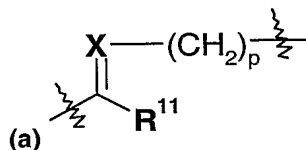
- 6 -

or when  $\mathbf{R}^3$  is a group of Formula (IIa) or (IIb), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

or when  $\mathbf{R}^3$  is a group of Formula (IIa), (IIb), (IIc) or (IId), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

5 **B** is selected from:

- (i) a direct bond;
- (ii) a group of Formula (IV)



Formula (IV)

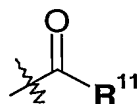
10 wherein:

**X** is selected from N, CH or a saturated heterocyclic ring;

wherein at position (a) Formula (IV) is attached to the nitrogen atom and the  $(\text{CH}_2)_p$  group is attached to  $\mathbf{R}^8$ ; and

- (iii) a group independently selected from: optionally substituted  $\text{C}_{1-6}$ alkylene, optionally substituted  $\text{C}_{3-7}$ cycloalkyl, optionally substituted  $\text{C}_{3-6}$ alkenylene, optionally substituted  $\text{C}_{3-6}$ alkynyl,  $\text{C}_{1-6}$ alkoxy,  $(\text{C}_{1-5}\text{alkyl})_{\text{aa}}\text{-S(O}_n\text{)-}(\text{C}_{1-5}\text{alkyl})_{\text{bb-}}$ ,  $(\text{C}_{1-5}\text{alkyl})_{\text{aa}}\text{-O-}(\text{C}_{1-5}\text{alkyl})_{\text{bb-}}$  or  $(\text{C}_{1-5}\text{alkyl})_{\text{aa}}\text{-N(R}^{15}\text{)-}(\text{C}_{1-5}\text{alkyl})_{\text{bb}}$ , wherein  $\mathbf{R}^{15}$  and the  $(\text{C}_{1-5}\text{alkyl})_{\text{aa}}$  or  $(\text{C}_{1-5}\text{alkyl})_{\text{bb}}$  chain can be joined to form a ring;

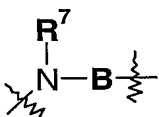
or the group  $\text{-B-R}^8$  represents a group of Formula (V)

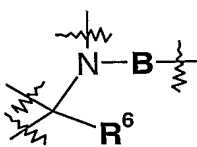


Formula (V);

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or the group  together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms;

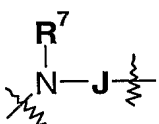
or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

5 **E** is -O-, -S(O<sub>n</sub>), -C(O)-, -NR<sup>15</sup>- or -C(R<sup>9</sup>R<sup>10</sup>)<sub>q</sub>;

**F** is -E(CH<sub>2</sub>)<sub>r</sub>- or -(CH<sub>2</sub>)<sub>r</sub>E -;

**G** is selected from: hydrogen, halo, CN, NO<sub>2</sub>, N, O, S(O<sub>n</sub>), C(O), C(R<sup>9</sup>R<sup>10</sup>)<sub>t</sub>, optionally substituted C<sub>2-6</sub>alkenylene, optionally substituted C<sub>2-6</sub>alkynylene, optionally substituted heterocyclyl or a direct bond to R<sup>18</sup>,

10 **J** is a group of the formula: -(CH<sub>2</sub>)<sub>s</sub>-L-(CH<sub>2</sub>)<sub>s</sub>- wherein when s is greater than 0, the alkylene group is optionally substituted,

or the group  together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms;

**K** is selected from: a direct bond, -(CH<sub>2</sub>)<sub>s1</sub>-, -(CH<sub>2</sub>)<sub>s1</sub>-O-(CH<sub>2</sub>)<sub>s2</sub>-, -(CH<sub>2</sub>)<sub>s1</sub>-C(O)-(CH<sub>2</sub>)<sub>s2</sub>-,

15 -(CH<sub>2</sub>)<sub>s1</sub>-S(O<sub>n</sub>)-(CH<sub>2</sub>)<sub>s2</sub>-, -(CH<sub>2</sub>)<sub>s1</sub>-N(R<sup>18</sup>)-(CH<sub>2</sub>)<sub>s2</sub>-, -(CH<sub>2</sub>)<sub>s1</sub>-C(O)N(R<sup>9</sup>)-(CH<sub>2</sub>)<sub>s2</sub>-,

-(CH<sub>2</sub>)<sub>s1</sub>-N(R<sup>9</sup>)C(O)-(CH<sub>2</sub>)<sub>s2</sub>-, -(CH<sub>2</sub>)<sub>s1</sub>-N(R<sup>9</sup>)C(O)N(R<sup>9</sup>)-(CH<sub>2</sub>)<sub>s2</sub>-,

-(CH<sub>2</sub>)<sub>s1</sub>-OC(O)-(CH<sub>2</sub>)<sub>s2</sub>-, -(CH<sub>2</sub>)<sub>s1</sub>-C(O)O-(CH<sub>2</sub>)<sub>s2</sub>-, -(CH<sub>2</sub>)<sub>s1</sub>-N(R<sup>9</sup>)C(O)O-(CH<sub>2</sub>)<sub>s2</sub>-,

-(CH<sub>2</sub>)<sub>s1</sub>-OC(O)N(R<sup>9</sup>)-(CH<sub>2</sub>)<sub>s2</sub>-, -(CH<sub>2</sub>)<sub>s1</sub>-OS(O<sub>n</sub>)-(CH<sub>2</sub>)<sub>s2</sub>-, or

-(CH<sub>2</sub>)<sub>s1</sub>-S(O<sub>n</sub>)-O-(CH<sub>2</sub>)<sub>s2</sub>-, -(CH<sub>2</sub>)<sub>s1</sub>-S(O)<sub>2</sub>N(R<sup>9</sup>)-(CH<sub>2</sub>)<sub>s2</sub>-,

20 -(CH<sub>2</sub>)<sub>s1</sub>-N(R<sup>9</sup>)S(O)<sub>2</sub>-(CH<sub>2</sub>)<sub>s2</sub>-; wherein the -(CH<sub>2</sub>)<sub>s1</sub>- and -(CH<sub>2</sub>)<sub>s2</sub>- groups are independently optionally substituted by hydroxy or C<sub>1-4</sub>alkyl;

**L** is selected from optionally substituted aryl or optionally substituted heterocyclyl;

**m** is an integer from 0 to 4;

**n** is an integer from 0 to 2;

25 **p** is an integer from 0 to 4;

**q** is an integer from 0 to 4;

**r** is an integer from 0 to 4;



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**s** is an integer from 0 to 4;

**s1** and **s2** are independently selected from an integer from 0 to 4, and

**s1+s2** is less than or equal to 4; and

**t** is an integer from 0 to 4;

5 **aa** and **bb** are independently selected from 0 or 1;

**cc** is an integer from 0 to 2;

with the proviso that

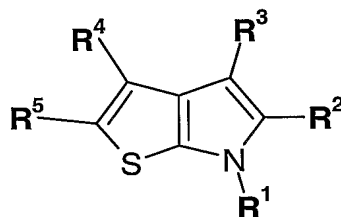
(i) when **G** is hydrogen, halo, CN or NO<sub>2</sub>, then **R**<sup>17</sup> and **R**<sup>18</sup> are both absent;

10 (ii) when **G** is O, S(O<sub>n</sub>), C(O) or C(**R**<sup>11</sup>**R**<sup>12</sup>)<sub>t</sub> then **G** is substituted by a single group independently selected from the definition of **R**<sup>17</sup> or **R**<sup>18</sup> and when **G** is a direct bond to **R**<sup>18</sup> then **G** is substituted by a single group selected from **R**<sup>18</sup>; and

(iii) when **R**<sup>3</sup> is a group of Formula (IIb), **B** is a group of Formula (IV), **R**<sup>8</sup> is selected from group (i) or (ii) above, **R**<sup>11</sup> is a group of the formula N(**R**<sup>10</sup>**R**<sup>11</sup>) and **R**<sup>1</sup>, **R**<sup>2</sup> and **R**<sup>5</sup> are as defined above then **R**<sup>4</sup> cannot be hydrogen;

15 or a salt, pro-drug or solvate thereof.

According to a further feature of the first aspect of the invention there is provided a compound of Formula (Ia),



Formula (Ia)

20

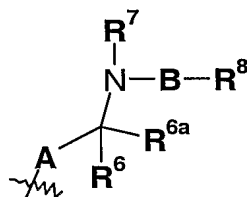
wherein:

**R**<sup>1</sup> is selected from: hydrogen, optionally-substituted C<sub>1-6</sub>alkyl, optionally substituted

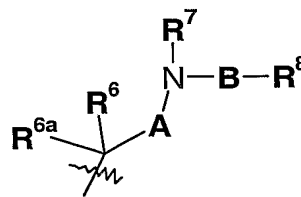
C<sub>1-6</sub>alkanoyl, optionally substituted aryl or optionally-substituted arylC<sub>1-6</sub>alkyl;

**R**<sup>2</sup> is an optionally-substituted mono or bi-cyclic aromatic ring;

25 **R**<sup>3</sup> is selected from a group of Formula (IIa) to Formula (IIf):

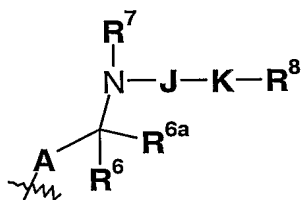


Formula (IIa)

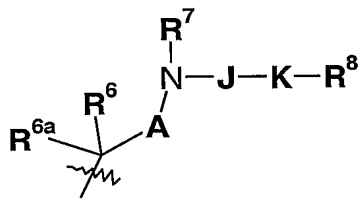


Formula (IIb)

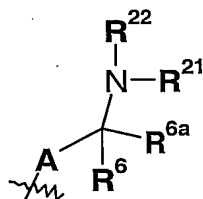
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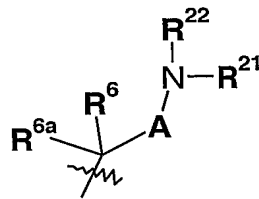
Formula (IIc)



Formula (IIId)

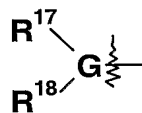


Formula (IIe)



Formula (IIIf)

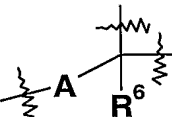
- 5 **R<sup>4</sup>** is selected from: hydrogen, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted aryl, C<sub>1-3</sub>perfluoroalkyl, cyano, nitro, halo, **R<sup>9</sup>O(CH<sub>2</sub>)<sub>m</sub>-**, **R<sup>9</sup>C(O)N(R<sup>10</sup>)-**, **R<sup>9</sup>R<sup>10</sup>NC(O)N(R<sup>10</sup>)-**, **R<sup>9</sup>S(O<sub>n</sub>)-** or or **R<sup>9</sup>R<sup>10</sup>NC(O)-(CR<sup>9</sup>R<sup>10</sup>)<sub>t</sub>-**;  
**R<sup>5</sup>** is a group of Formula (III):

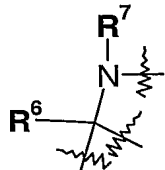


10

Formula (III)

- R<sup>6</sup>** and **R<sup>6a</sup>** are independently selected from hydrogen, optionally substituted C<sub>1-6</sub>alkyl, optionally-substituted aryl or optionally substituted arylC<sub>1-6</sub>alkyl, or **R<sup>6</sup>** and **R<sup>6a</sup>** taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms, or **R<sup>6</sup>** and **R<sup>6a</sup>** taken together and the carbon atom to which they are attached form a carbonyl group;

or when A is not a direct bond the group  forms a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

## - 10 -

$R^7$  is selected from: hydrogen, optionally-substituted  $C_{1-6}$ alkyl, optionally-substituted aryl $C_{1-6}$ alkyl, optionally-substituted aryl, optionally substituted heterocyclyl, optionally substituted heterocyclyl $C_{1-6}$ alkyl,  $R^9OC_{1-6}$ alkyl-,  $R^9R^{10}NC_{1-6}$ alkyl-,  $R^9R^{10}NC(O)C_{1-6}$ alkyl,  $-C(NR^9R^{10})=NH$ ;

5 or when  $R^3$  is a group of Formula (IIc) or (IId)  $R^7$  is of the formula  $-J-K-R^8$ ;

$R^8$  is selected from:

- (i) hydrogen,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl, halo $C_{1-6}$ alkyl,  $C_{1-4}$ alkoxy $C_{1-4}$ alkyl, hydroxy, hydroxy $C_{1-6}$ alkyl, cyano, N- $C_{1-4}$ alkylamino, N,N-di- $C_{1-4}$ alkylamino,  $C_{1-6}$ alkyl- $S(O_n)-$ ,  $-O-R^b$ ,  $-NR^bR^c$ ,  $-C(O)-R^b$ ,  $-C(O)O-R^b$ ,  $-CONR^bR^c$  or  
 10  $NH-C(O)-R^b$ ,  
 where  $R^b$  and  $R^c$  are independently selected from hydrogen and  $C_{1-4}$ alkyl optionally substituted with hydroxy, amino, N- $C_{1-4}$ alkylamino, N,N-di- $C_{1-4}$ alkylamino, HO- $C_{2-4}$ alkyl-NH- or HO- $C_{2-4}$ alkyl-N( $C_{1-4}$ alkyl)-;
- (ii) nitro when  $B$  is a group of Formula (IV) and  $X$  is CH and  $p$  is 0;
- 15 (iii)  $C_{3-7}$ cycloalkyl, aryl or aryl $C_{1-6}$ alkyl each of which is optionally substituted by  $R^{12}$ ,  $R^{13}$  and  $R^{14}$ ;
- (iv)  $-(Q)-$ aryl,  $-(Q)-$ heterocyclyl,  $-(Q)-$ aryl, each of which is optionally substituted by  $R^{12}$ ,  $R^{13}$  and  $R^{14}$   
 wherein  $-(Q)-$  is selected from  $E$ ,  $F$  or a direct bond;
- 20 (v) heterocyclyl or heterocyclyl $C_{1-6}$ alkyl each of which is optionally substituted by  $R^{12}$ ,  $R^{13}$  and  $R^{14}$ ;
- (vi) a group selected from  $R^{12}$ ,  $R^{13}$  and  $R^{14}$ ;

$R^9$  and  $R^{10}$  are independently selected from: hydrogen, hydroxy, optionally substituted  $C_{1-6}$ alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$ alkyl, an optionally  
 25 substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclyl $C_{1-6}$ alkyl or  $R^9$  and  $R^{10}$  taken together can form an optionally substituted ring of 3-9 atoms or  $R^9$  and  $R^{10}$  taken together with the carbon atom to which they are attached form a carbonyl group;

$R^{11}$  is selected from: hydrogen, optionally substituted  $C_{1-6}$ alkyl, or  $N(R^9R^{10})$ ;

30  $R^{12}$  is selected from: hydrogen, hydroxy,  $R^{17}R^{18}N-$ , optionally substituted  $C_{1-6}$ alkyl- $SO_2N(R^9)-$ , optionally substituted aryl- $SO_2N(R^9)-$ ,  $C_{1-3}$ perfluoroalkyl- $SO_2N(R^9)-$ ; optionally substituted  $C_{1-6}$ alkyl- $N(R^9)SO_2-$ , optionally substituted aryl- $N(R^9)SO_2-$ ,  $C_{1-3}$ perfluoroalkyl- $N(R^9)SO_2-$  optionally substituted

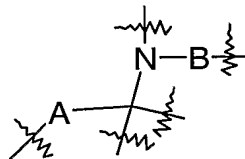
## - 11 -


- $C_{1-6}$ alkanoyl- $N(R^9)SO_2-$ ; optionally substituted aryl- $C(O)N(R^9)SO_2-$ , optionally substituted  $C_{1-6}$ alkyl- $S(O_n)-$ , optionally substituted aryl- $S(O_n)-$ ,  $C_{1-3}$ perfluoroalkyl-,  $C_{1-3}$ perfluoroalkoxy, optionally substituted  $C_{1-6}$ alkoxy, carboxy, halo, nitro or cyano;  $R^{13}$  and  $R^{14}$  are independently selected from: hydrogen, optionally substituted  $C_{1-6}$ alkyl, optionally substituted  $C_{2-6}$ alkenyl, cyano, nitro,  $C_{1-3}$ perfluoroalkyl-,  $C_{1-3}$ perfluoroalkoxy, optionally substituted aryl, optionally substituted aryl $C_{1-6}$ alkyl,  $R^9O(CH_2)_s-$ ,  $R^9(O)O(CH_2)_s-$ ,  $R^9OC(O)(CH_2)_s-$ ,  $R^{16}S(O_n)(CH_2)_s-$ ,  $R^9R^{10}NC(O)(CH_2)_s-$  or halo;
- $R^{15}$  is selected from: hydrogen, optionally substituted  $C_{1-6}$ alkyl,  $R^{19}OC(O)-$ ,  $R^9R^{10}NC(O)-$ ,  $R^9C(O)-$ ,  $R^9S(O_n)-$ ;
- $R^{16}$  is selected from: hydrogen,  $C_{1-6}$ alkyl,  $C_{1-3}$ perfluoroalkyl or optionally-substituted aryl;  $R^{17}$  is independently selected from: hydrogen, hydroxy, cyano or optionally substituted  $C_{1-6}$ alkyl;
- $R^{18}$  is a group of formula  $R^{18a}-C(R^9R^{10})_{0-1}-$  wherein  $R^{18a}$  is selected from:  $R^{19}OC(O)-$ ,  $R^9R^{10}NC(O)-$ ,  $R^9R^{10}N-$ ,  $R^9C(O)-$ ,  $R^9C(O)N(R^{10})-$ ,  $R^9R^{10}NC(O)-$ ,  $R^9R^{10}NC(O)N(R^{10})-$ ,  $R^9SO_2N(R^{10})-$ ,  $R^9R^{10}NSO_2N(R^{10})-$ ,  $R^9C(O)O-$ ,  $R^9OC(O)-$ ,  $R^9R^{10}NC(O)O-$ ,  $R^9O-$ ,  $R^9S(O_n)-$ ,  $R^9R^{10}NS(O_n)-$ , optionally substituted  $C_{1-6}$ alkyl, optionally substituted heterocyclyl;
- or  $R^{17}$  and  $R^{18}$  when taken together form an optionally substituted carbocyclic ring of 3-7 atoms or optionally substituted heterocyclyl;
- $R^{19}$  is selected from: hydrogen, optionally substituted  $C_{1-6}$ alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$ alkyl, optionally substituted  $C_{3-7}$ cycloalkyl, optionally substituted heterocyclyl or optionally substituted heterocyclyl $C_{1-6}$ alkyl;
- $R^{20}$  is selected from  $R^{12}$  or  $R^{13}$ ;
- $R^{21}$  and  $R^{22}$  are independently selected from hydrogen, optionally substituted  $C_{1-6}$ alkyl, optionally substituted  $C_{3-7}$ cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclyl $C_{1-6}$ alkyl, optionally substituted  $C_{3-6}$ alkenyl, optionally substituted  $C_{3-6}$ alkynyl,  $-(C_{1-5}alkyl)_{aa}-S(O_n)-(C_{1-5}alkyl)_{bb}-$ ,  $R^9R^{10}NC_{2-6}alkyl$ ,  $R^9OC_{2-6}alkyl$  or  $R^9R^{10}NC(O)C_{2-6}alkyl$ , with the proviso that  $R^9$  and  $R^{10}$  independently or taken together are not optionally substituted aryl or optionally substituted aryl $C_{1-6}$ alkyl; or
- $R^{21}$  and  $R^{22}$  taken together form an optionally substituted non-aromatic heterocyclic ring;

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**A** is selected from:

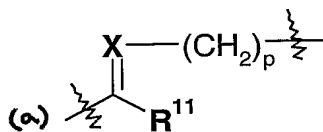
- (i) a direct bond;
- (ii) optionally-substituted C<sub>1-5</sub>alkylene wherein the optional substituents are independently selected from: optionally-substituted C<sub>1-6</sub>alkyl  
 5 optionally-substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl or substituted arylC<sub>1-6</sub>alkyl;
- (iii) a carbocyclic ring of 3-7 atoms;
- (iv) a carbonyl group;

or when **R**<sup>3</sup> is a group of Formula (IIa) or (IIb), the group  forms a  
 10 heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

or when **R**<sup>3</sup> is a group of Formula (IIa), (IIb), (IIc) or (IId), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

**B** is selected from:

- (i) a direct bond;
- (ii) a group of Formula (IV)



Formula (IV)

wherein:

**X** is selected from N, CH or a saturated heterocyclic ring;

20 wherein at position (a) Formula (IV) is attached to the nitrogen atom and the (CH<sub>2</sub>)<sub>p</sub> group is attached to **R**<sup>8</sup>; and

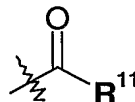
- (iii) a group independently selected from: optionally substituted C<sub>1-6</sub>alkylene, optionally substituted C<sub>3-7</sub>cycloalkyl, optionally substituted C<sub>3-6</sub>alkenylene, optionally substituted C<sub>3-6</sub>alkynyl, C<sub>1-6</sub>alkoxy, (C<sub>1-5</sub>alkyl)<sub>aa</sub>-S(O<sub>n</sub>)-(C<sub>1-5</sub>alkyl)<sub>bb</sub>,

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$(C_{1-5}\text{alkyl})_{aa}-O-(C_{1-5}\text{alkyl})_{bb}-$  or  $(C_{1-5}\text{alkyl})_{aa}-N(R^{15})-(C_{1-5}\text{alkyl})_{bb}$ ,

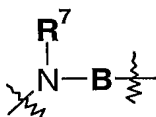
wherein  $R^{15}$  and the  $(C_{1-5}\text{alkyl})_{aa}$  or  $(C_{1-5}\text{alkyl})_{bb}$  chain can be joined to form a ring;

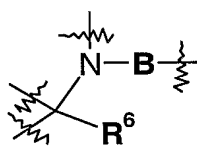
or the group  $-B-R^8$  represents a group of Formula (V)



Formula (V);

5

or the group  together forms a heterocyclic ring containing 5-7 carbons atoms;

or the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

10 **E** is  $-O-$ ,  $-S(O_n)-$ ,  $-C(O)-$ ,  $-NR^{15}-$  or  $-C(R^9R^{10})_q-$ ;

**F** is  $-E(CH_2)_r-$  or  $-(CH_2)_rE-$ ;

**G** is selected from: hydrogen, halo, CN,  $NO_2$ , N, O,  $S(O_n)$ ,  $C(O)$ ,  $C(R^9R^{10})_t$ , optionally substituted  $C_{2-6}$ alkenylene, optionally substituted  $C_{2-6}$ alkynylene, optionally substituted heterocyclyl or a direct bond to  $R^{18}$ ,

15 **J** is a group of the formula:  $-(CH_2)_s-L-(CH_2)_s-$  wherein when  $s$  is greater than 0, the alkylene group is optionally substituted

**K** is selected from: a direct bond,  $-O-(CH_2)_s-$ ,  $-C(O)-(CH_2)_s-$ ,  $-S(O_n)-(CH_2)_s-$ ,  $-N(R^{18})-(CH_2)_s-$ ,  $-OC(O)-(CH_2)_s-$ ,  $-C(O)O-(CH_2)_s-$ ,  $-OS(O_n)-(CH_2)_s-$ , or  $-S(O_n)-O-(CH_2)_s-$ ;

20 **L** is selected from optionally substituted aryl or optionally substituted heterocyclyl;

**n** is an integer between 0 and 2;

**p** is an integer between 0 and 4;

**q** is an integer between 0 and 4;

**r** is an integer between 0 and 4;

25 **s** is an integer between 0 and 4; and

**t** is an integer between 0 and 4;

**aa** and **bb** are independently selected from 0 or 1

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with the proviso that

- (i) when **G** is hydrogen, halo, CN or NO<sub>2</sub>, then **R**<sup>17</sup> and **R**<sup>18</sup> are both absent;
- (ii) when **G** is O, S(O<sub>n</sub>), C(O) or C(**R**<sup>11**R**<sup>12</sup>)<sub>t</sub> then **G** is substituted by a single group independently selected from the definition of **R**<sup>17</sup> or **R**<sup>18</sup> and when **G** is a direct  
5 bond to **R**<sup>18</sup> then **G** is substituted by a single group selected from **R**<sup>18</sup>; and  
or a salt, pro-drug or solvate thereof.</sup>

According to a further feature of the first aspect of the invention there is provided a pharmaceutical formulation comprising a compound of Formula (I) or Formula (Ia), or salt, pro-drug or solvate thereof, and a pharmaceutically acceptable diluent or carrier.

10 According to a further feature of the first aspect of the invention there is provided the following uses of a compound of Formula (I) or Formula (Ia), or salt, pro-drug or solvate thereof:

- (a) the use in the manufacture of a medicament for antagonising gonadotropin releasing hormone activity;
- 15 (b) the use in the manufacture of a medicament for administration to a patient, for reducing the secretion of luteinizing hormone by the pituitary gland of the patient; and
- (c) the use in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient, preferably a sex hormone related condition selected from prostate cancer and pre-  
20 menopausal breast cancer.

According to a further aspect of the invention there is provided a method of antagonising gonadotropin releasing hormone activity in a patient, comprising administering a compound of Formula (I) or Formula (Ia), or salt, pro-drug or solvate thereof, to a patient.

Whilst pharmaceutically-acceptable salts of compounds of the invention are preferred,  
25 other non-pharmaceutically-acceptable salts of compounds of the invention may also be useful, for example in the preparation of pharmaceutically-acceptable salts of compounds of the invention.

Whilst the invention comprises compounds of the invention, and salts, pro-drugs or solvates thereof, in a further embodiment of the invention, the invention comprises  
30 compounds of the invention and salts thereof.

In the present specification, unless otherwise indicated, an **alkyl**, **alkylene**, **alkenyl** or **alkynyl** moiety may be linear or branched. The term "**alkylene**" refers to the group -CH<sub>2</sub>-. Thus, C<sub>8</sub> alkylene for example is -(CH<sub>2</sub>)<sub>8</sub>-.

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The term '**propylene**' refers to trimethylene and the branched alkyl chains  $-\text{CH}(\text{CH}_3)\text{CH}_2-$  and  $-\text{CH}_2-\text{CH}(\text{CH}_3)-$ . The straight chain propylene di-radical is preferred, i.e.  $-\text{CH}_2\text{CH}_2\text{CH}_2-$ . Specific propylene radicals refer to the particular structure, thus the term, propyl-2-ene refers to the group  $-\text{CH}_2-\text{CH}(\text{CH}_3)-$ . Similar notation is used for other divalent  
5 alkyl chains such as butylene.

The term '**2-propenyl**' refers to the group  $-\text{CH}_2-\text{CH}=\text{CH}-$ .

The term "**aryl**" refers to phenyl or naphthyl.

The term "**carbamoyl**" refers to the group  $-\text{C}(\text{O})\text{NH}_2$ .

The term "**halo**" refers to fluoro, chloro, bromo or iodo.


10 The term "**heterocyclyl**" or "**heterocyclic ring**" refers to a 4-12 membered, preferably 5-10 membered, aromatic mono or bicyclic ring or a 4-12 membered, preferably 5-10 membered, saturated or partially saturated mono or bicyclic ring, said aromatic, saturated or partially unsaturated rings containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur, linked via ring carbon atoms or ring nitrogen atoms where a  
15 bond from a nitrogen is allowed, for example no bond is possible to the nitrogen of a pyridine ring, but a bond is possible through the 1-nitrogen of a pyrazole ring. Examples of 5- or 6-membered aromatic heterocyclic rings include pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4 oxadiazolyl, isothiazolyl, thiazolyl and thienyl. A 9 or 10 membered bicyclic aromatic heterocyclic ring is  
20 an aromatic bicyclic ring system comprising a 6-membered ring fused to either a 5 membered ring or another 6 membered ring. Examples of 5/6 and 6/6 bicyclic ring systems include benzofuranyl, benzimidazolyl, benzthiophenyl, benzthiazolyl, benzisothiazolyl, benzoxazolyl, benzisoxazolyl, indolyl, pyridoimidazolyl, pyrimidoimidazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, phthalazinyl, cinnolinyl and naphthyridinyl. Examples of  
25 saturated or partially saturated heterocyclic rings include pyrrolinyl, pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, dihydropyridinyl and dihydropyrimidinyl. This definition further comprises sulphur-containing rings wherein the sulphur atom has been oxidised to an S(O) or S(O<sub>2</sub>) group.

The term "**aromatic ring**" refers to a 5-10 membered aromatic mono or bicyclic ring  
30 optionally containing up to 5 heteroatoms independently selected from nitrogen, oxygen or sulphur. Examples of such "aromatic rings" include: phenyl, pyrrolyl, furanyl, imidazolyl, triazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyridinyl, isoxazolyl, oxazolyl, 1,2,4



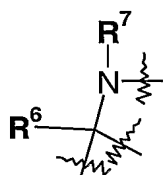
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oxadiazolyl, isothiazolyl, thiazolyl and thienyl. Preferred aromatic rings include phenyl, thienyl and pyridyl.

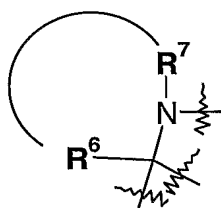
The symbol  denotes where the respective group is linked to the remainder of the molecule.

- 5 For the avoidance of doubt where two groups or integers appear within the same definition, for example,  $-(CH_2)_5-L-(CH_2)_5-$  or  $R^9R^{10}NSO_2N(R^{10})-$ , then these can be the same or different.

For the avoidance of doubt, where several groups together form a ring, for example:



- ‘the group forms a heterocyclic ring containing 3-7 carbon atoms and one or  
10 more heteroatoms’, then the groups shown cyclises to form a ring, i.e



the component of which are defined by the definitions of the groups which form the ring, thus in the above example the ring would include a nitrogen atom. For example in Example 2 this group forms a piperazine ring.

- The term **C<sub>1-3</sub>perfluoroalkyl** refers to a C<sub>1-3</sub>alkyl chain in which all hydrogens have  
15 been replaced with a fluorine atom. Examples of **C<sub>1-3</sub>perfluoroalkyl** include trifluoromethyl, pentafluoroethyl and 1-trifluoromethyl-1,2,2,2-tetrafluoroethyl-. Preferably **C<sub>1-3</sub>perfluoroalkyl** is trifluoromethyl.

- Examples of **C<sub>1-8</sub>alkyl** include: methyl, ethyl, propyl, isopropyl, butyl, *iso*-butyl, *tert*-butyl and 2-methyl-pentyl; example of **C<sub>1-8</sub>alkylene** include: methylene, ethylene and  
20 2-methyl-propylene; examples of **C<sub>1-6</sub>alkenyl** include allyl (2-propenyl) and 2-butenyl, examples of **C<sub>1-6</sub>alkynyl** 2-propynyl and 3-butylnyl, examples of **haloC<sub>1-6</sub>alkyl** include fluoroethyl, chloropropyl and bromobutyl, examples of **hydroxyC<sub>1-6</sub>alkyl** include hydroxymethyl, hydroxyethyl and hydroxybutyl, examples of **C<sub>1-8</sub>alkoxy** include methoxy, ethoxy and butyloxy; examples of **C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl** include methoxyethyl, propoxybutyl  
25 and propoxymethyl, examples of **C<sub>1-6</sub>alkanoyl** include formyl, ethanoyl, propanoyl or pentanoyl, examples of **N-C<sub>1-4</sub>alkylamino** include N-methylamino and N-ethylamino;

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examples of **N,N-di-C<sub>1-4</sub>alkylamino** include N,N-dimethylaminoethyl, N,N-di-methylaminopropyl and N,N-dipropylaminoethyl, examples of **HO-C<sub>2-4</sub>alkyl-NH** include hydroxymethylamino hydroxyethylamino and hydroxypropylamino, examples of **HO-C<sub>2-4</sub>alkyl-N(C<sub>1-4</sub>alkyl)** include N-methyl-hydroxymethylamino,

5 N-ethyl-hydroxyethylamino, and N-propyl-hydroxypropylamino, examples of **C<sub>1-6</sub>alkyl-S(O<sub>n</sub>)-methylthio**, methylsulphinyl, ethylsulphinyl, ethylsulphonyl and propylsulphonyl, include examples of **arylC<sub>1-6</sub>alkyl** include benzyl, phenethyl and phenylbutyl, examples of **heterocyclylC<sub>1-6</sub>alkyl** include pyrrolidin-1-yl ethyl, imidazolylethyl, pyridylmethyl and pyrimidinylethyl.

10 It is to be understood that, insofar as certain of the compounds of the invention may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses the property of antagonizing gonadotropin releasing hormone (GnRH) activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, activity of these compounds may be evaluated using the standard laboratory techniques referred to hereinafter.

The invention also relates to any and all tautomeric forms of the compounds of the different features of the invention that possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms which possess the property of antagonizing gonadotropin releasing hormone (GnRH) activity.

25 Preferred compounds of Formula (I) are those wherein any one of the following or any combination of the following apply.

Preferably **R<sup>1</sup>** is selected from hydrogen or optionally substituted C<sub>1-6</sub>alkyl. More preferably **R<sup>1</sup>** represents hydrogen or unsubstituted C<sub>1-6</sub>alkyl. Yet more preferably **R<sup>1</sup>** represents hydrogen, methyl, ethyl or *tert*-butyl. Most preferably **R<sup>1</sup>** represents hydrogen.

30 Preferably optional substituents on **R<sup>1</sup>** are independently selected from: optionally-substituted C<sub>1-6</sub>alkyl, optionally-substituted C<sub>2-6</sub>alkenyl, cyano, nitro, C<sub>1-3</sub>perfluoroalkyl, C<sub>1-3</sub>perfluoroalkoxy, optionally-substituted aryl, optionally-substituted arylC<sub>1-6</sub>alkyl, **R<sup>9</sup>O(CH<sub>2</sub>)<sub>v</sub>-**; **R<sup>9</sup>C(O)O(CH<sub>2</sub>)<sub>v</sub>-**, **R<sup>9</sup>OC(O)(CH<sub>2</sub>)<sub>v</sub>-**, **R<sup>16</sup>S(O<sub>n</sub>)(CH<sub>2</sub>)<sub>v</sub>-**,

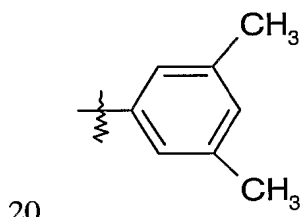
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$R^9R^{10}NC(O)(CH_2)_v$ -, or halo wherein  $v$  is an integer between 0 and 4, and where 2 optional substituents are present together they can optionally form a  $C_{3-7}$ carbocyclic ring or a heterocyclic ring.

Preferably  $R^2$  is an optionally substituted monocyclic aromatic ring structure. Most  
5 preferably  $R^2$  represents optionally substituted phenyl.

Preferably optional substituents on  $R^2$  are independently selected from: optionally substituted  $C_{1-6}$ alkyl, optionally substituted  $C_{2-6}$ alkenyl, cyano, nitro,  $C_{1-3}$ perfluoroalkyl,  $C_{1-3}$ perfluoroalkoxy, optionally substituted aryl, optionally substituted aryl $C_{1-6}$ alkyl,  $R^9O(CH_2)_p$ -,  $R^9C(O)O(CH_2)_w$ -,  $R^9OC(O)(CH_2)_w$ -,  $R^{16}S(O_n)(CH_2)_w$ -,  $R^9R^{10}NC(O)(CH_2)_w$ -,  
10  $R^9R^{10}N$ - or halo; wherein  $w$  is an integer between 0 and 4 and  $R^9$  and  $R^{10}$  are as defined above. Further preferably the optional substituents on  $R^2$  are independently selected from cyano,  $R^eR^fN$ -, optionally substituted  $C_{1-6}$ alkyl (preferably,  $C_{1-4}$ alkyl, eg, methyl or ethyl), optionally substituted  $C_{1-6}$ alkoxy (preferably,  $C_{1-4}$ alkoxy, eg, methoxy, ethoxy or *tert*-butoxy) or halo (eg, F, Br or Cl) wherein  $R^e$  and  $R^f$  are independently selected from hydrogen,  
15  $C_{1-6}$ alkyl or aryl. Yet further preferably optional substituents on  $R^2$  are independently selected from methyl, ethyl, methoxy, ethoxy, *tert*-butoxy, F or Cl. Most preferably optional substituents on  $R^2$  are independently selected from methyl, F or Cl. Preferably  $R^2$  bears 1, 2 or 3 substituents.

Most preferably  $R^2$  represents



Preferably  $R^3$  is selected from a group of Formula (IIa), Formula (IIb), Formula (IIc) or Formula (IId). Most preferably  $R^3$  is a group of Formula (IIc) or Formula (IId).

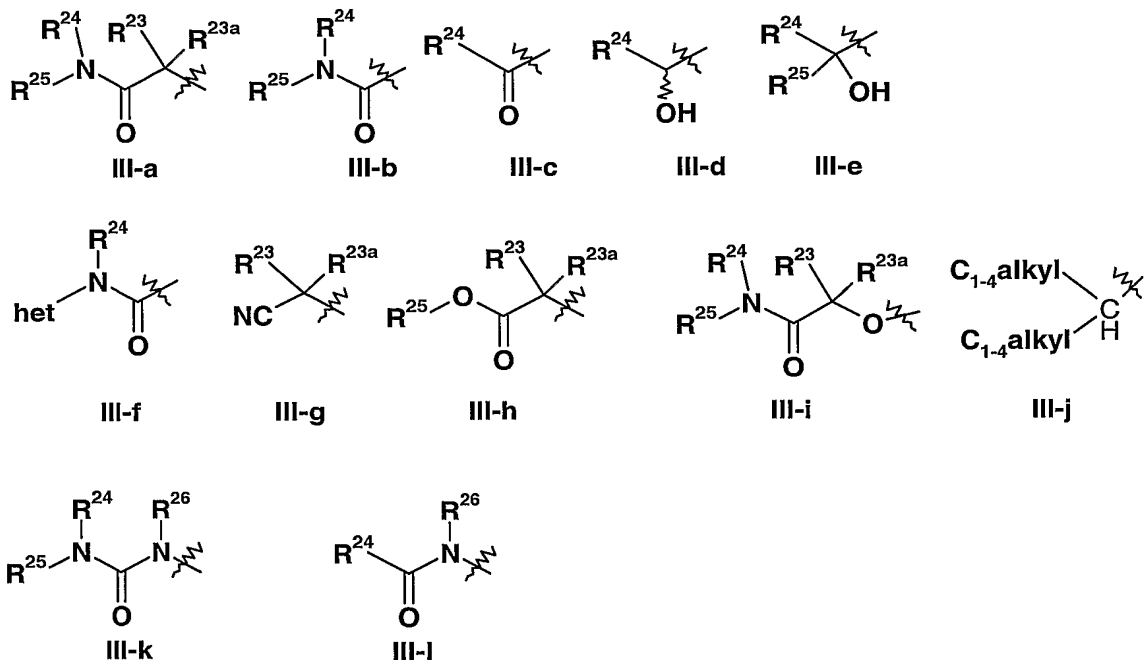
Preferably  $R^4$  is selected from hydrogen or  $C_{1-4}$ alkyl. Most preferably  $R^4$  is hydrogen. Preferably the group of Formula (III):



Formula (III)

is selected from one of a group of Formula III-a to III-l;

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wherein:

**het** represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

5 **R<sup>23</sup>** and **R<sup>23a</sup>** are independently selected from:

- (i) hydrogen, fluoro or optionally substituted C<sub>1-8</sub>alkyl; or
- (ii) **R<sup>23</sup>** and **R<sup>23a</sup>** together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring;

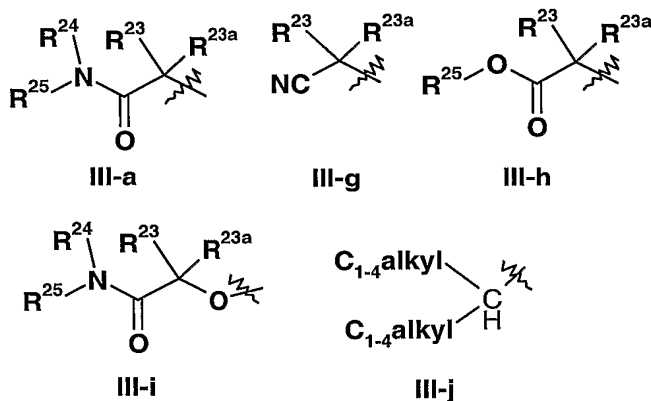
**R<sup>24</sup>** and **R<sup>25</sup>** are selected from:

- 10 (i) **R<sup>24</sup>** selected from hydrogen; optionally substituted C<sub>1-8</sub>alkyl; optionally substituted aryl; -**R<sup>d</sup>**-Ar, where **R<sup>d</sup>** represents C<sub>1-8</sub>alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; and **R<sup>25</sup>** is selected from hydrogen; optionally substituted C<sub>1-8</sub>alkyl and optionally substituted aryl;
- 15 (ii) wherein the group of Formula (III) represents a group of Formula **III-a**, **III-b** or **III-i**, then the group NR<sup>24</sup>(-R<sup>25</sup>) represents an optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

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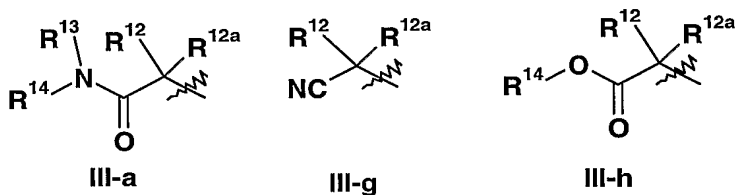
- (iii) wherein the group of Formula (III) represents structure **III-e**,  
 represents an optionally substituted 3- to 8- membered heterocyclic ring  
 optionally containing from 1 to 4 heteroatoms independently selected from O, N  
 and S;  $R^{26}$  is selected from hydrogen or  $C_{1-4}$ alkyl. Preferably  $R^{26}$  is selected from  
 5 hydrogen, methyl or ethyl. Most preferably  $R^{26}$  is hydrogen.

Preferably the group of Formula (III) is selected from a group of Formula **III-a**, **III-g**,  
**III-h**, or **III-i**:



wherein  $R^{23}$ ,  $R^{23a}$ ,  $R^{24}$  and  $R^{25}$  are as defined above.

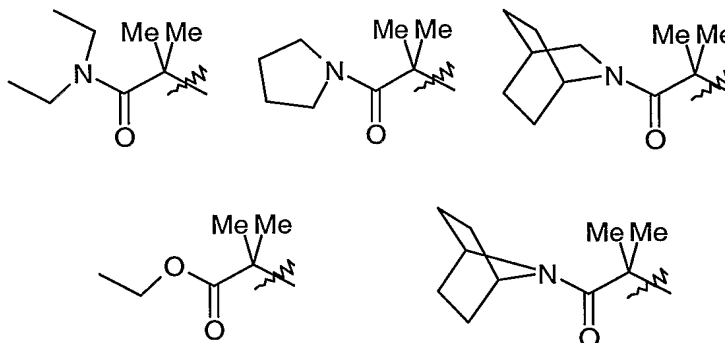
- 10 Further preferably the group of Formula (III) is selected from one of the following groups:



wherein  $R^{23}$ ,  $R^{23a}$ ,  $R^{24}$  and  $R^{25}$  are as defined above.

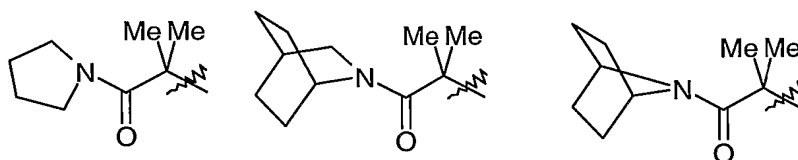
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Yet further preferably the group of Formula (III) is selected from one of the following groups:

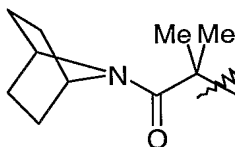


wherein Me represents methyl.

5 Yet further preferably the group of Formula (III) is selected from one of the following groups:



Most preferably the group of Formula (III) is:

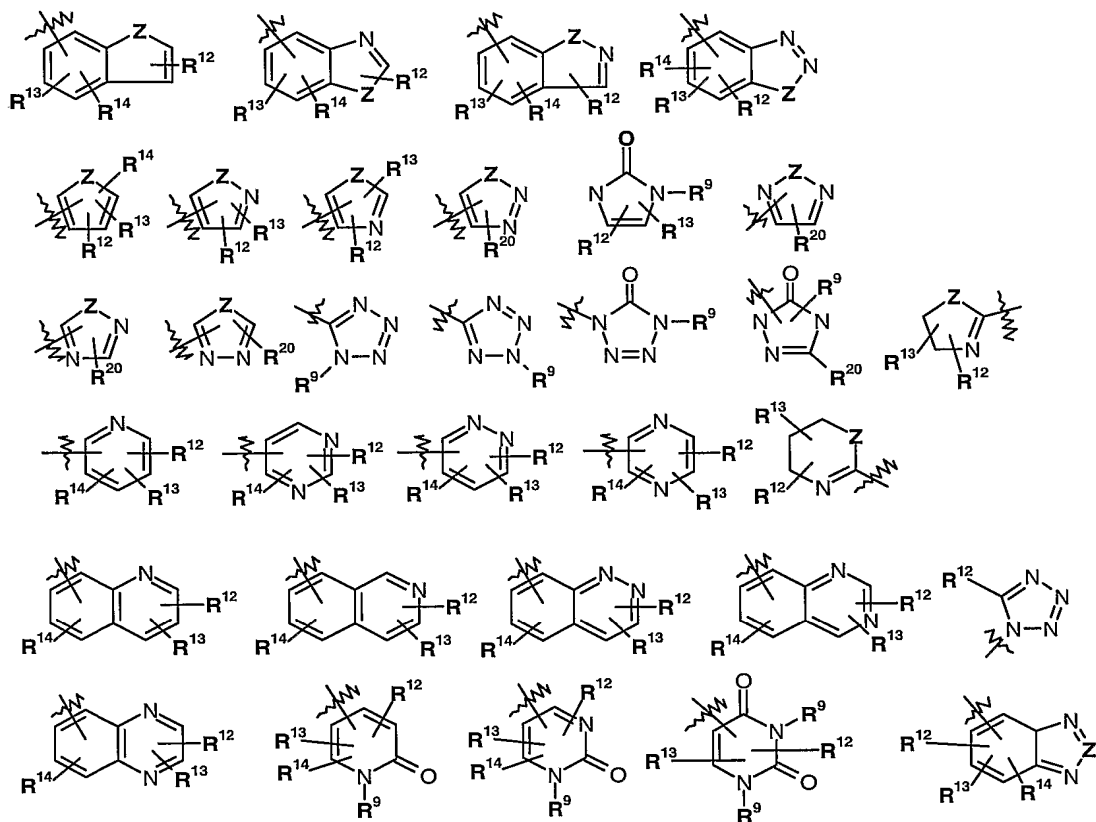


10 Preferably **R<sup>6</sup>** and **R<sup>6a</sup>** are independently selected from hydrogen, fluoro or optionally substituted C<sub>1-6</sub>alkyl. Preferably **R<sup>6</sup>** and **R<sup>6a</sup>** are independently selected from hydrogen and unsubstituted C<sub>1-6</sub>alkyl. Yet more preferably **R<sup>6</sup>** and **R<sup>6a</sup>** are independently selected from hydrogen or methyl. Most preferably **R<sup>6</sup>** and **R<sup>6a</sup>** are both hydrogen.

Preferably **R<sup>7</sup>** is selected from: hydrogen or C<sub>1-4</sub>alkyl. More preferably **R<sup>7</sup>** is hydrogen  
15 or methyl. Most preferably **R<sup>7</sup>** is hydrogen.

When **R<sup>8</sup>** is heterocyclyl then **R<sup>8</sup>** is preferably selected from one of the following groups:

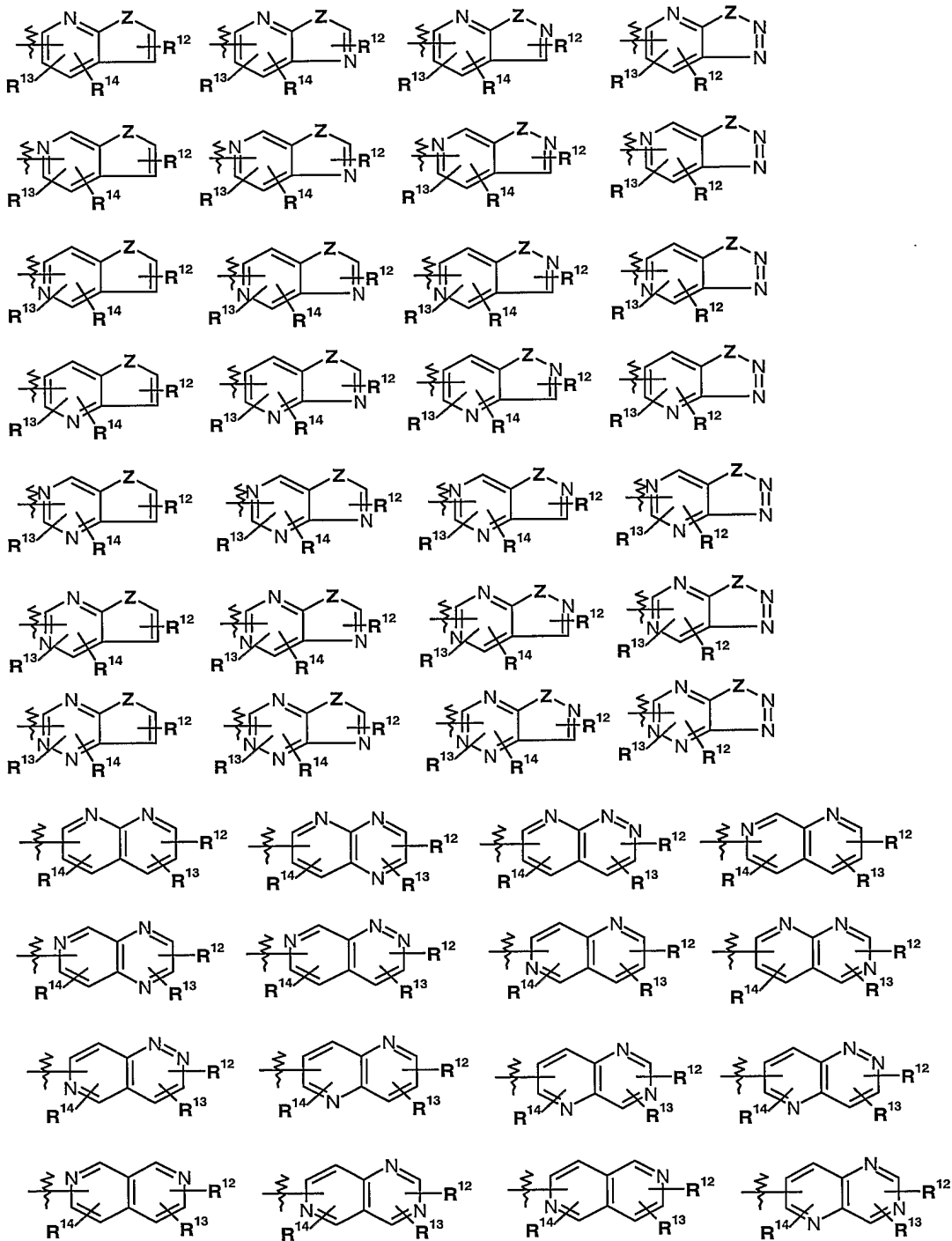
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wherein  $Z$  is selected from: O, S or  $N(R^9)$ ,  $R^{20}$  is selected from any group within the definitions of  $R^{12}$  and  $R^{13}$ , and  $R^9$ ,  $R^{12}$ ,  $R^{13}$  and  $R^{14}$  are as defined above.

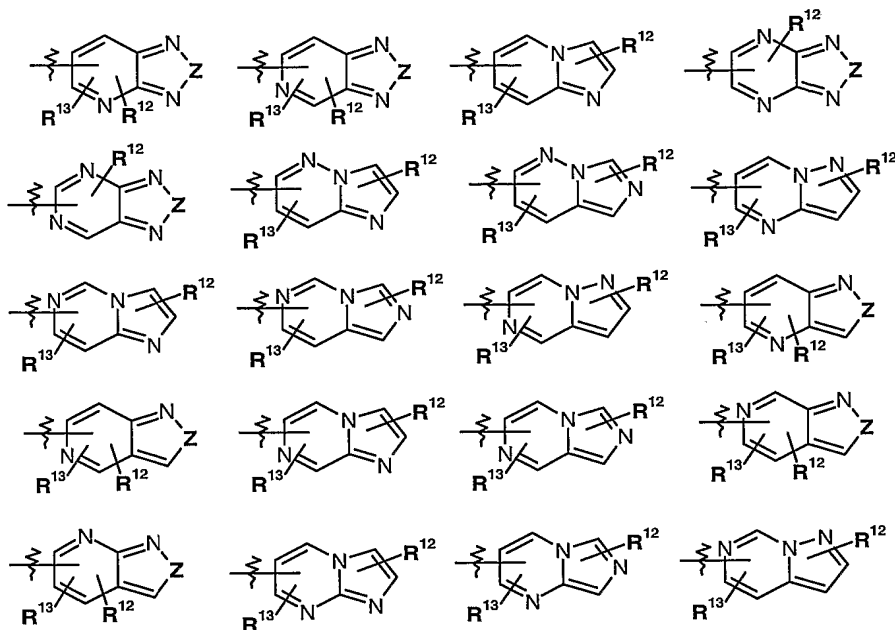
In a further embodiment of the invention when  $R^8$  is heterocyclyl then  $R^8$  is preferably  
 5 selected from one of the following groups:

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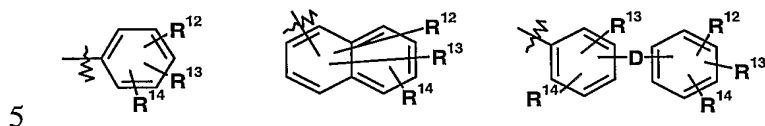


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wherein **Z** is selected from: O, S or N(**R**<sup>9</sup>) and **R**<sup>9</sup>, **R**<sup>12</sup> and **R**<sup>13</sup> are as defined above.

When **R**<sup>8</sup> is aryl or aryl-(**Q**)-aryl optionally substituted by **R**<sup>12</sup>, **R**<sup>13</sup> and **R**<sup>14</sup>, **R**<sup>8</sup> is preferably selected one of the following groups:



wherein **D** is selected from group **E**, group **F** or a direct bond;

Preferably **R**<sup>8</sup> is selected from

- (i) hydrogen, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, haloC<sub>1-6</sub>alkyl, hydroxy, cyano, C<sub>1-6</sub>alkylS(O)<sub>n</sub>-, -O-**R**<sup>b</sup>, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, -C(O)-**R**<sup>b</sup>, C(O)O-**R**<sup>b</sup>, -NH-C(O)-**R**<sup>b</sup>, N,N-di-C<sub>1-4</sub>alkylamino, -S(O)<sub>n</sub>N**R**<sup>b</sup>**R**<sup>c</sup>
- 10

where **R**<sup>b</sup> and **R**<sup>c</sup> are independently selected from hydrogen and C<sub>1-6</sub>alkyl, and **n** is 0, 1 or 2;

- (ii) -(**Q**)-aryl, wherein aryl is optionally substituted;

- (iii) optionally substituted C<sub>4-7</sub>heterocyclyl,

- 15 more preferably optionally substituted C<sub>4-7</sub>heterocyclyl selected from: aziriny, azetidiny, pyrrolidiny, pyrazoliny, pyrazolidiny, imidazoliny, imidazolidiny, piperidiny, piperaziny, hexahydropyrimidiny, hexahydropyridaziny, hexahydrotriaziny, tetrahydrotriaziny, dihydrotriaziny, tetrahydrofurany, dioxolany, tetrahydropyrany, dioxany, trioxany, tetrahydrothieny, 1-oxotetrahydrothieny, 20 1,1-dioxotetrahydrothieny tetrahydrothiopyran, 1-oxotetrahydrothiopyran,

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1,1-dioxotetrahydrothiopyran, dithianyl, trithianyl, morpholinyl, oxathiolanyl, oxathianyl, thiomorpholinyl, thiazinanyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, thiazolidinyl, pyrrolyl, imidazolyl, triazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, thiazolyl, thiadiazolyl, thiadiazinyl, oxazolyl, isoxazolyl, oxadiazolyl, furazanyl, octahydropyrrolopyrrolyl, octahydropyrrolopyrrolyl, benzotriazolyl, dihydrobenzotriazolyl, indolyl, indolinyl, benzimidazolyl, 2,3-dihydrobenzimidazolyl, benzotriazolyl 2,3-dihydro benzotriazolyl quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, benzodioxolyl, tetrahydrodioxolopyrrolyl, 1,5-dioxo-9-azaspiro[5.5]undecanyl and 8-oxa-3-azabicyclooctanyl; or

(iv) optionally substituted C<sub>3-7</sub>carbocyclyl;

Further preferably **R**<sup>8</sup> is selected from

(i) hydrogen, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, haloC<sub>1-6</sub>alkyl, hydroxy, cyano, C<sub>1-6</sub>alkylS(O)<sub>n</sub>-, -O-**R**<sup>b</sup>, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, -C(O)-**R**<sup>b</sup>, C(O)O-**R**<sup>b</sup>, -NH-C(O)-**R**<sup>b</sup>, N,N-di-C<sub>1-4</sub>alkylamino, -S(O)<sub>n</sub>NR<sup>b</sup>R<sup>c</sup>

where **R**<sup>b</sup> and **R**<sup>c</sup> are independently selected from hydrogen and C<sub>1-6</sub>alkyl, and **n** is 0, 1 or 2;

(ii) -(Q)-aryl, wherein aryl is optionally substituted;

(iii) optionally substituted C<sub>4-7</sub>heterocyclyl selected from: azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl, morpholinyl, tetrahydrothienyl, 1,1-dioxotetrahydrothienyl, thiomorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, imidazolyl, thiazolyl, isoxazolyl, pyridyl, pyrimidinyl, tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrolyl, 1,5-dioxo-9-azaspiro[5.5]undecanyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, benzodioxolyl, 2,3-dihydrobenzotriazolyl and octahydropyrrolo[3,4-c]pyrrolyl; or

(iv) optionally substituted C<sub>3-7</sub>carbocyclyl;

Yet further preferably **R**<sup>8</sup> is selected from

(i) hydrogen, methyl, isopropyl, *t*-butyl, 1-methylethyl, allyl, fluoroethyl, hydroxy, cyano, ethylsulphonyl, methoxy, 1-methyl-2-methoxyethyl, acetyl, *t*-butoxycarbonyl, acetyl amino, dimethyl amino, diethyl amino, (1-methylethyl) amino, isopropyl amino or aminosulphonyl;

(ii) optionally substituted phenyl;

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- (iii) optionally substituted C<sub>4-7</sub>heterocyclyl selected from:azetidiny, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl, morpholinyl, tetrahydrothienyl, 1,1-dioxotetrahydrothienyl, thiomorpholinyl, 1-oxo-thiomorpholinyl, 1,1-dioxo-thiomorpholinyl, imidazolyl, thiazolyl, isoxazolyl, pyridyl, pyrimidinyl, tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyrrolyl, 1,5-dioxa-9-azaspiro[5.5]undecanyl, 8-oxa-3-azabicyclo[3.2.1]octanyl, benzodioxolyl, 2,3-dihydrobenzotriazolyl or octahydropyrrolo[3,4-c]pyrrolyl; or
- (iv) optionally substituted C<sub>3-7</sub>carbocyclyl selected from:cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl

10 Yet further preferably **R**<sup>8</sup> is selected from optionally substituted C<sub>4-7</sub>heterocyclyl selected from:piperidinyl or piperazinyl, azetidiny, imidazolyl and thiazolyl.

Most preferably **R**<sup>8</sup> is optionally substituted C<sub>4-7</sub>heterocyclyl selected from:piperidinyl or piperazinyl.

In another embodiment of the invention **R**<sup>8</sup> is selected from hydrogen, cyano, C<sub>1-4</sub>alkyl (more preferably methyl), C<sub>2-6</sub>alkynyl (more preferably 2-propynyl), hydroxyC<sub>1-6</sub>alkyl (more preferably hydroxyethyl), C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl (more preferably methoxyethyl), haloC<sub>1-6</sub>alkyl (more preferably fluoroethyl), C<sub>1-4</sub>alkanoyl (more preferably formyl), C<sub>1-4</sub>alkoxycarbonyl (more preferably butyloxycarbonyl), N,N-di-C<sub>1-4</sub>alkylamino (more preferably N,N-dimethylaminoethyl and N,N-dimethylaminopropyl), C<sub>1-6</sub>alkyl-S(O<sub>n</sub>)- (more preferably ethylsulphonyl), cyclopentyl, phenyl, benzyl, cyanophenyl, pyrrolidinyl, pyrrolidinylethyl, imidazolyl, imidazolylC<sub>1-6</sub>alkyl (more preferably imidazolylethyl), thiazolyl, pyridyl, pyridylC<sub>1-6</sub>alkyl (more preferably pyridylmethyl) or pyrimidyl wherein a phenyl or heterocyclyl ring is optionally substituted by C<sub>1-4</sub>alkyl.

When **R**<sup>9</sup> and/or **R**<sup>10</sup> is a component of group **G**, **R**<sup>9</sup> and **R**<sup>10</sup> are preferably independently selected from hydrogen, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl or **R**<sup>9</sup> and **R**<sup>10</sup> forms C<sub>3-7</sub>cycloalkyl or heterocyclyl. Further preferably hydrogen or C<sub>1-4</sub>alkyl. Most preferably hydrogen or methyl. Most preferably both **R**<sup>9</sup> and **R**<sup>10</sup> are methyl.

When **R**<sup>9</sup> and/or **R**<sup>10</sup> is a component of group **R**<sup>18</sup>, **R**<sup>9</sup> and **R**<sup>10</sup> are preferably independently selected from hydrogen, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl or **R**<sup>9</sup> and **R**<sup>10</sup> forms C<sub>3-7</sub>cycloalkyl or heterocyclyl. Further preferably when **R**<sup>9</sup> is a component of group **R**<sup>18</sup>, **R**<sup>9</sup> is preferably heterocyclyl. Most preferably pyrrolidinyl, 7-azabicyclo[2.2.1]hept-7-yl or 3-azabicyclo[3.2.2]nonyl.

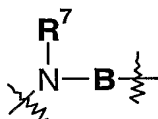
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Preferably  $R^{17}$  is hydrogen, hydroxy, cyano or is absent. Most preferably  $R^{17}$  is absent.

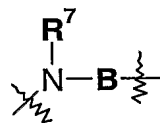
Preferably  $R^{18}$  is selected from hydrogen,  $R^9N(R^{10})C(O)-$ ,  $R^9C(O)-$ ,  $R^9OC(O)-$  or  $R^{18a}-C(R^9R^{10})-$  wherein  $R^{18a}$  is  $R^9N(R^{10})C(O)-$ . Further preferably  $R^9C(O)-$ . Most preferably  $R^9C(O)-$  wherein  $R^9$  is heterocyclyl.

5 Preferably **A** is selected from a direct bond, optionally substituted  $C_{1-5}$ alkylene, carbonyl or  $-C(O)-C(R^dR^d)-$ , wherein  $R^d$  is independently selected from hydrogen and  $C_{1-2}$ alkyl. Further preferably **A** is a direct bond,  $C_{1-5}$ alkylene optionally substituted with  $C_{1-4}$ alkyl, carbonyl or carbonylmethyl. Yet further preferably **A** is a direct bond, unsubstituted  $C_{1-2}$ alkylene or carbonyl. Most preferably **A** is methylene.

10 Preferably **B** is selected from optionally substituted  $C_{1-6}$ alkylene or the group



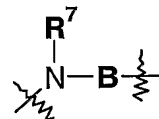
forms an optionally substituted  $C_{4-7}$ heterocyclic ring.



More preferably **B** is  $C_{1-6}$ alkylene or the group

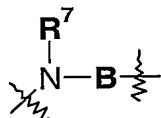
forms an optionally

substituted saturated  $C_{4-7}$ heterocyclic ring.



Further preferably **B** is unsubstituted  $C_{1-6}$ alkylene or the group forms an optionally substituted saturated  $C_{4-7}$ heterocyclic ring selected from: azetidiny, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl, hexahydropyridazinyl, hexahydrotriazinyl, tetrahydrotriazinyl, dihydrotriazinyl, morpholinyl, thiomorpholinyl, thiazinanyl, thiazolidinyl, 1,5-dioxo-9-azaspiro[5.5]undecanyl or octahydropyrrolopyrrolyl, wherein the optional substituents are selected from. cyano, hydroxy, oxo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkanoyl,  $R^9OC(O)(CH_2)_w-$ ,  $R^9R^{10}NC(O)(CH_2)_w-$  or halo, wherein  $w$  is an integer between 0 and 4 and  $R^9$  and  $R^{10}$  are as defined above. Further preferably the optional substituents are selected from: cyano, hydroxy, oxo,  $C_{1-4}$ alkyl,  $C_{1-4}$ alkoxy and  $C_{1-4}$ alkanoyl.

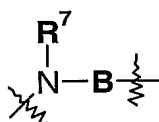
Yet further preferably **B** is selected from: ethylene, propylene or butylene or the group



25 forms an optionally substituted saturated  $C_{4-7}$ heterocyclic ring selected from:

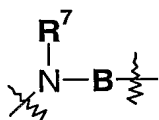
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azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, 1,5-dioxo-9-azaspiro[5.5]undecanyl or octahydropyrrolopyrrolyl, wherein the optional substituents are selected from oxo.



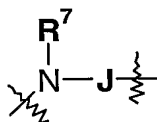
- Most preferably the group forms an optionally substituted saturated C<sub>4-7</sub>heterocyclic ring selected from: piperidinyl or piperazinyl, wherein the optional
- 5 substituents are selected from oxo.

In another embodiment of the invention **B** is selected from optionally substituted

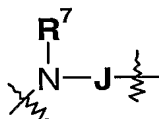


- C<sub>1-6</sub>alkylene or the group forms a C<sub>5-7</sub>heterocyclic ring. Preferably unsubstituted C<sub>6</sub>alkylene or a C<sub>5-7</sub>heterocyclic saturated ring. Most preferably methylene, ethylene, propylene, butylene or piperazinyl.
- 10 Preferably **G** is a direct bond, -O- or -C(R<sup>9</sup>R<sup>10</sup>)-. More preferably -C(R<sup>9</sup>R<sup>10</sup>)-. Most preferably -C(CH<sub>3</sub>)<sub>2</sub>-.

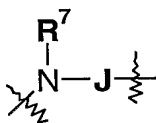
When **R**<sup>3</sup> is selected from a group of Formula (IIc) or Formula (IId) then the group



preferably forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms.

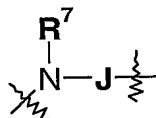


- 15 More preferably the group forms an optionally substituted saturated C<sub>4-7</sub>heterocyclic ring.

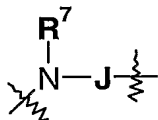


- Further preferably the group forms an optionally substituted saturated C<sub>4-7</sub>heterocyclic ring selected from: azetidiny, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, piperidinyl, piperazinyl, hexahydropyrimidinyl,
- 20 hexahydropyridazinyl, hexahydrotriazinyl, tetrahydrotriazinyl, dihydrotriazinyl, morpholinyl, thiomorpholinyl, thiazinanyl, thiazolidinyl or octahydropyrrolopyrrolyl, wherein the optional substituents are selected from oxo.

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Further preferably the group forms an optionally substituted saturated  $C_{4-7}$  heterocyclic ring selected from: pyrrolidinyl, piperidinyl or piperazinyl, wherein the optional substituents are selected from oxo.



- Most preferably the group forms an optionally substituted saturated  $C_{4-7}$  heterocyclic ring selected from: piperidinyl or piperazinyl, wherein the optional substituents are selected from oxo.

Preferably **K** is selected from:  $-(CH_2)_s-$ ,  $-(CH_2)_s-O-(CH_2)_s-$ ,  $-(CH_2)_s-C(O)-(CH_2)_s-$ ,  $-(CH_2)_s-N(R^{18})-(CH_2)_s-$ ,  $-(CH_2)_s-C(O)N(R^{18})-(CH_2)_s-$ ,  $-(CH_2)_s-N(R^{18})C(O)-(CH_2)_s-$ ,  $-(CH_2)_s-S(O)_2N(R^{18})-(CH_2)_s-$ , or  $-(CH_2)_s-NHS(O)_2-(CH_2)_s-$ ,

- 10 wherein **s** is independently selected from 0, 1, 2, 3 or 4, **R**<sup>18</sup> is selected from hydrogen or  $C_{1-4}$  alkyl (preferably hydrogen) and the  $-(CH_2)_s-$  group is optionally substituted by hydroxy or  $C_{1-4}$  alkyl.

More preferably **K** is selected from:  $-(CH_2)_{s1}-$ ,  $-(CH_2)_{s1}-O-(CH_2)_{s2}-$ ,  $-(CH_2)_{s1}-C(O)-$ ,  $-C(O)-(CH_2)_{s2}-$ ,  $-(CH_2)_{s1}-N(R^{18})-$ ,  $-(CH_2)_{s1}-C(O)N(R^{18})-$ ,  $-(CH_2)_{s1}-N(R^{18})C(O)-(CH_2)_{s2}-$ ,  
15  $-(CH_2)_{s1}-S(O)_2N(R^{18})-$  or  $-(CH_2)_{s1}-NHS(O)_2-$ ,

wherein **s**<sub>1</sub> and **s**<sub>2</sub> are independently selected from 0, 1, 2, 3 or 4 and **s**<sub>1</sub>+**s**<sub>2</sub> is less than or equal to 4, **R**<sup>18</sup> is selected from hydrogen or  $C_{1-4}$  alkyl (preferably hydrogen) and the  $-(CH_2)_s-$  group is optionally substituted by hydroxy or  $C_{1-4}$  alkyl.

- More preferably **K** is selected from: methylene, ethylene, propylene, oxy,  
20 2-hydroxypropylene, carbonyl, methylcarbonyl, ethylcarbonyl, (methyl)methylcarbonyl, (ethyl)methylcarbonyl, carbonylmethylene, carbonylethylene, ethoxyethylene, amino, 2-hydroxypropylamino, carbonylamino, methylcarbonylamino, aminocarbonyl, methylaminocarbonyl, methylaminocarbonylmethyl, propylsulphonylamino or methylaminosulphonyl.

- 25 Further preferably **K** is selected from: methylene, carbonyl, carbonylamino, methylcarbonylamino, aminocarbonyl, methylaminocarbonyl or methylaminosulphonyl.

Most preferably **K** is selected from: methylene, carbonyl or methylcarbonylamino;

Preferably optional substituents on heterocyclyl groups in **R**<sup>8</sup>, **R**<sup>9</sup>, **R**<sup>10</sup>, **R**<sup>18</sup> and **R**<sup>19</sup> or on heterocyclyl groups formed when **R**<sup>17</sup> and **R**<sup>18</sup> together form a heterocyclic ring are selected

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from: optionally substituted C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkanoyl, optionally substituted C<sub>2-6</sub>alkenyl, cyano, nitro, C<sub>1-3</sub>perfluoroalkyl, C<sub>1-3</sub>perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl,  $R^9O(CH_2)_p-$ ,  $R^9C(O)O(CH_2)_w-$ ,  $R^9OC(O)(CH_2)_w-$ ,  $R^{16}S(O_n)(CH_2)_w-$ ,  $R^9R^{10}NC(O)(CH_2)_w-$  or halo; wherein w is an integer between 0 and 4 and

5  $p$ ,  $R^9$ ,  $R^{10}$  and  $R^{16}$  are as defined above.

More preferably optional substituents on  $R^8$  are selected from: cyano, hydroxy, oxo, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl,  $R^9OC(O)(CH_2)_w-$ ,  $R^9R^{10}NC(O)(CH_2)_w-$  or halo, wherein w is an integer between 0 and 4 and  $R^9$  and  $R^{10}$  are as defined above.

Further preferably optional substituents on  $R^8$  are selected from: cyano, hydroxy, oxo,

10 C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy and C<sub>1-4</sub>alkanoyl.

Most preferably optional substituents on  $R^8$  are selected from: cyano, oxo, methyl, methoxy and acetyl.

Preferably the optional substituents on alkyl, alkenyl, alkynyl, cycloalkyl and aryl groups are independently selected from C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>3-7</sub>cycloalkyl, optionally

15 substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl, hydroxy, oxo, cyano, C<sub>1-6</sub>alkoxy, halo (preferably fluoro),  $R^{16}S(O_n)(CH_2)_w-$ ,  $R^9OC(O)-$ , optionally substituted arylC<sub>1-3</sub>alkoxy wherein  $R^9$  is as defined above.

Preferably the optional substituents on optionally substituted aryl and arylC<sub>1-6</sub>alkyl groups are selected from: optionally substituted C<sub>1-6</sub>alkyl, optionally substituted C<sub>2-6</sub>alkenyl,

20 cyano, nitro, halo (preferably fluoro), C<sub>1-3</sub>perfluoroalkyl, C<sub>1-3</sub>perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl,  $R^9O(CH_2)_p-$ ,  $R^9C(O)O(CH_2)_w-$ ,  $R^9OC(O)(CH_2)_w-$ ,  $R^{16}S(O_n)(CH_2)_w-$ ,  $R^9R^{10}NC(O)(CH_2)_w-$  or halo; wherein w is an integer between 0 and 4 and n,  $R^9$  and  $R^{10}$  are as defined above..

In preferences for heterocyclyl in  $R^8$  the nitrogen atoms contained in  $R^8$  heteroaromatic

25 rings exist either as drawn or, where chemically allowed, in their oxidised (N→O, N-OH) state.

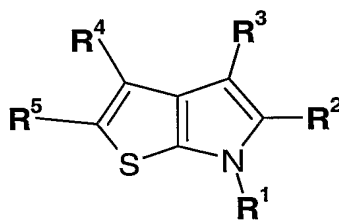
Where optional substitution is mentioned at various places the optional substituents also comprise the following definition which refers to one, two, three or more optional substituents. Unless otherwise indicated above (i.e., where a list of optional substituents is

30 specifically listed within a definition), each substituent can be independently selected from C<sub>1-8</sub>alkyl (eg, C<sub>2-6</sub>alkyl, and most preferably methyl, ethyl or *tert*-butyl); C<sub>3-8</sub>cycloalkoxy, preferably cyclopropoxy, cyclobutoxy or cyclopentoxo; C<sub>1-6</sub>alkoxy, preferably methoxy or C<sub>2-4</sub>alkoxy; halo, preferably Cl or F; Hal<sub>3</sub>C-, Hal<sub>2</sub>CH-, HalCH<sub>2</sub>-, Hal<sub>3</sub>CO-, Hal<sub>2</sub>CHO or Hal

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CH<sub>2</sub>O, wherein Hal represents halo (preferably F); **R<sup>g</sup>**CH<sub>2</sub>O-, **R<sup>h</sup>**C(O)N(R)-, **R<sup>h</sup>**SO<sub>2</sub>N(R)- or **R<sup>g</sup>**-**R<sup>h</sup>**N-, wherein **R<sup>g</sup>** and **R<sup>h</sup>** independently represent hydrogen or C<sub>1-8</sub>alkyl (preferably methyl or C<sub>2-6</sub>alkyl or C<sub>2-4</sub>alkyl), or **R<sup>g</sup>**-**R<sup>h</sup>**N- represents an optionally substituted C<sub>3-8</sub>, preferably C<sub>3-6</sub>, heterocyclic ring optionally containing from 1 to 3 further heteroatoms  
 5 independently selected from O, N and S; hydrogen; or **R<sup>k</sup>**C(O)O- or **R<sup>k</sup>**C(O)-, **R<sup>k</sup>** representing hydrogen, optionally substituted phenyl or C<sub>1-6</sub>alkyl (preferably methyl, ethyl, *iso*-propyl or *tert*-butyl). For optional substitution of the heterocyclic ring represented by **R<sup>g</sup>**-**R<sup>h</sup>**N-, at least one (eg, one, two or three) substituents may be provided independently selected from C<sub>1-6</sub>alkyl (eg, C<sub>2-4</sub>alkyl, more preferably methyl); phenyl; CF<sub>3</sub>O-; F<sub>2</sub>CHO-; C<sub>1-8</sub>alkoxy,  
 10 preferably methoxy, ethoxy or C<sub>3-6</sub>alkoxy; C<sub>1-8</sub>alkoxyC(O), preferably methoxycarbonyl, ethoxycarbonyl, *tert*-butoxycarbonyl or C<sub>3-6</sub>alkoxyC(O)-; phenoxycarbonyl; phenoxy; C<sub>1-8</sub>alkanoyl, preferably acetyl, ethanoyl or C<sub>3-6</sub>alkylanoyl; carboxy; C<sub>1-8</sub>alkylS(O<sub>*nn*</sub>) wherein *nn* is an integer between 0 and 2, preferably methylthio, ethylthio, C<sub>3-6</sub>alkylthio, methylsulphinyl, ethylsulphinyl, C<sub>3-6</sub>alkylsulphinyl, methylsulphonyl, ethylsulphonyl or  
 15 C<sub>3-6</sub>alkylsulphonyl; hydroxy; halo (eg, F, Cl or Br); **R<sup>m</sup>****R<sup>n</sup>**N- where **R<sup>m</sup>** and **R<sup>n</sup>** are independently hydrogen or C<sub>1-6</sub>alkyl (preferably C<sub>2-4</sub>alkyl, more preferably methyl, most preferably **R<sup>m</sup>**=**R<sup>n</sup>**=methyl); and nitro.

According to a further aspect of the invention there is provided a compound of Formula (Ib)



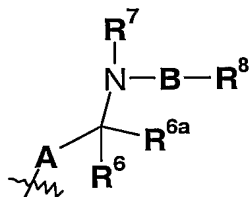
Formula (Ib)

wherein:

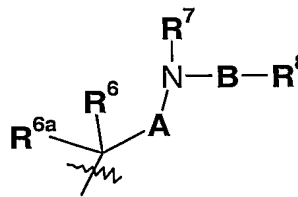
**R<sup>1</sup>** represents hydrogen or unsubstituted C<sub>1-6</sub>alkyl;

**R<sup>2</sup>** represents optionally substituted phenyl;

**R<sup>3</sup>** is selected from a group of Formula (IIa) to Formula (IId):



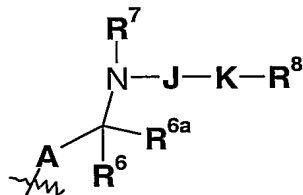
Formula (IIa)



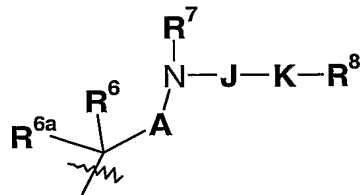
Formula (IIb)



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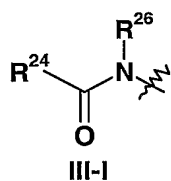
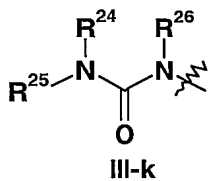
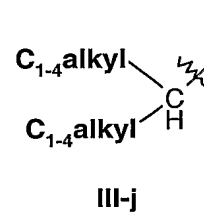
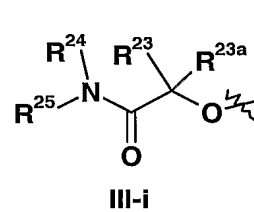
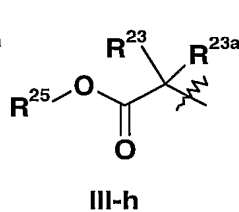
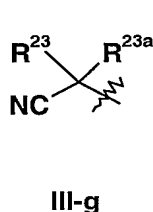
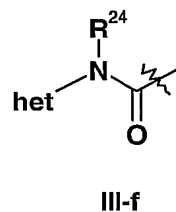
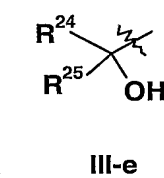
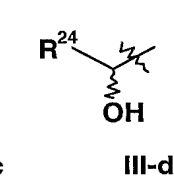
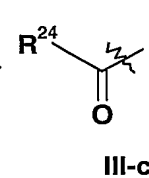
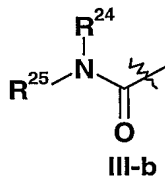
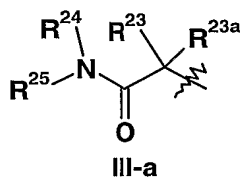
Formula (IIc)



Formula (IId)

$R^4$  is selected from hydrogen or  $C_{1-4}$ alkyl;

$R^5$  is selected from a one of a group of Formula III-a to III-j:



5

;

wherein:

**het** represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;

$R^{23}$  and  $R^{23a}$  are independently selected from:

- 10 (i) hydrogen, fluoro or optionally substituted  $C_{1-8}$ alkyl; or  
 (ii)  $R^{23}$  and  $R^{23a}$  together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring;

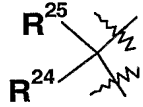
$R^{24}$  and  $R^{25}$  are selected from:

- 15 (i)  $R^{24}$  selected from hydrogen; optionally substituted  $C_{1-8}$ alkyl; optionally substituted aryl;  $-R^d$ -Ar, where  $R^d$  represents  $C_{1-8}$ alkylene and Ar represents optionally substituted aryl; and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms

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independently selected from O, N and S; and  $R^{25}$  is selected from hydrogen; optionally substituted  $C_{1-8}$ alkyl and optionally substituted aryl;

- (ii) wherein the group of Formula (III) represents a group of Formula **III-a**, **III-b** or **III-i**, then the group  $NR^{24}(-R^{25})$  represents an optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S; or

- (iii) wherein the group of Formula (III) represents structure **III-e**,  represents an optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

$R^{26}$  is selected from hydrogen or  $C_{1-4}$ alkyl.

$R^6$  and  $R^{6a}$  are independently selected from hydrogen, fluoro or optionally substituted  $C_{1-6}$ alkyl.

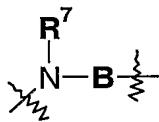
$R^7$  is selected from: hydrogen or  $C_{1-4}$ alkyl;

$R^8$  is selected from

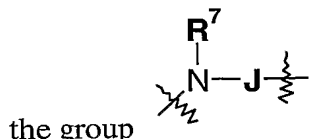
- (i) hydrogen,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl, halo $C_{1-6}$ alkyl, hydroxy, cyano,  $C_{1-6}$ alkyl $S(O)_n-$ ,  $-O-R^b$ ,  $C_{1-4}$ alkoxy $C_{1-4}$ alkyl,  $-C(O)-R^b$ ,  $C(O)O-R^b$ ,  $-NH-C(O)-R^b$ ,  $N,N$ -di- $C_{1-4}$ alkylamino or  $-S(O)_nNR^bR^c$  where  $R^b$  and  $R^c$  are independently selected from hydrogen and  $C_{1-6}$ alkyl, and  $n$  is 0, 1 or 2;
- (ii)  $-aryl$ , optionally substituted by up to 4 substituents selected from  $R^{12}$ ,  $R^{13}$  and  $R^{14}$ ;
- (iii)  $C_{4-7}$ heterocyclyl, optionally substituted by up to 4 substituents selected from  $R^{12}$ ,  $R^{13}$  and  $R^{14}$ ; or
- (iv)  $C_{3-7}$ carbocyclyl, optionally substituted by up to 4 substituents selected from  $R^{12}$ ,  $R^{13}$  and  $R^{14}$ ;

$R^9$  and  $R^{10}$  are independently selected from: hydrogen, hydroxy, optionally substituted  $C_{1-6}$ alkyl, optionally substituted aryl, optionally substituted aryl $C_{1-6}$ alkyl, an optionally substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclyl $C_{1-6}$ alkyl or  $R^9$  and  $R^{10}$  taken together can form an optionally substituted ring of 3-9 atoms or  $R^9$  and  $R^{10}$  taken together with the carbon atom to which they are attached form a carbonyl group;

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- R<sup>12</sup>** is selected from: hydrogen, hydroxy, **R<sup>17</sup>R<sup>18</sup>N(CH<sub>2</sub>)<sub>cc</sub>-**, **R<sup>17</sup>R<sup>18</sup>NC(O)(CH<sub>2</sub>)<sub>cc</sub>-**, optionally substituted C<sub>1-6</sub>alkyl- C(O)N(**R<sup>9</sup>**)(CH<sub>2</sub>)<sub>cc</sub>-, optionally substituted C<sub>1-6</sub>alkyl-SO<sub>2</sub>N(**R<sup>9</sup>**)-, optionally substituted aryl-SO<sub>2</sub>N(**R<sup>9</sup>**)-, C<sub>1-3</sub>perfluoroalkyl-SO<sub>2</sub>N(**R<sup>9</sup>**)-; optionally substituted C<sub>1-6</sub>alkyl-N(**R<sup>9</sup>**)SO<sub>2</sub>-, optionally substituted aryl-N(**R<sup>9</sup>**)SO<sub>2</sub>-, C<sub>1-3</sub>perfluoroalkyl-N(**R<sup>9</sup>**)SO<sub>2</sub>- optionally substituted C<sub>1-6</sub>alkanoyl-N(**R<sup>9</sup>**)SO<sub>2</sub>-; optionally substituted aryl-C(O)N(**R<sup>9</sup>**)SO<sub>2</sub>-, optionally substituted C<sub>1-6</sub>alkyl-S(O<sub>n</sub>) -, optionally substituted aryl-S(O<sub>n</sub>) -, C<sub>1-3</sub>perfluoroalkyl-, C<sub>1-3</sub>perfluoroalkoxy, optionally substituted C<sub>1-6</sub>alkoxy, carboxy, halo, nitro or cyano;
- R<sup>13</sup>** and **R<sup>14</sup>** are independently selected from: hydrogen, hydroxy, oxo, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted C<sub>1-6</sub>alkanoyl, optionally substituted C<sub>2-6</sub>alkenyl, cyano, nitro, C<sub>1-3</sub>perfluoroalkyl-, C<sub>1-3</sub>perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl, **R<sup>9</sup>O(CH<sub>2</sub>)<sub>s</sub>-**, **R<sup>9</sup>(O)O(CH<sub>2</sub>)<sub>s</sub>-**, **R<sup>9</sup>OC(O)(CH<sub>2</sub>)<sub>s</sub>-**, **R<sup>16</sup>S(O<sub>n</sub>)(CH<sub>2</sub>)<sub>s</sub>-**, **R<sup>9</sup>R<sup>10</sup>NC(O)(CH<sub>2</sub>)<sub>s</sub>-** or halo; **A** is selected from optionally substituted C<sub>1-5</sub>alkylene, carbonyl or -C(O)-C(**R<sup>d</sup>****R<sup>d</sup>**)-, wherein **R<sup>d</sup>** is independently selected from hydrogen and C<sub>1-2</sub>alkyl;
- R<sup>17</sup>** is independently selected from: hydrogen, hydroxy, cyano or optionally substituted C<sub>1-6</sub>alkyl;
- R<sup>18</sup>** is a group of formula **R<sup>18a</sup>-C(R<sup>9</sup>R<sup>10</sup>)<sub>0-1</sub>-** wherein **R<sup>18a</sup>** is selected from: **R<sup>9</sup>OC(O)-**, **R<sup>9</sup>R<sup>10</sup>NC(O)-**, **R<sup>9</sup>R<sup>10</sup>N-**, **R<sup>9</sup>C(O)-**, **R<sup>9</sup>C(O)N(R<sup>10</sup>)-**, **R<sup>9</sup>R<sup>10</sup>NC(O)-**, **R<sup>9</sup>R<sup>10</sup>NC(O)N(R<sup>10</sup>)-**, **R<sup>9</sup>SO<sub>2</sub>N(R<sup>10</sup>)-**, **R<sup>9</sup>R<sup>10</sup>NSO<sub>2</sub>N(R<sup>10</sup>)-**, **R<sup>9</sup>C(O)O-**, **R<sup>9</sup>OC(O)-**, **R<sup>9</sup>R<sup>10</sup>NC(O)O-**, **R<sup>9</sup>O-**, **R<sup>9</sup>S(O<sub>n</sub>)-**, **R<sup>9</sup>R<sup>10</sup>NS(O<sub>n</sub>) -**, hydrogen, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted heterocyclyl;
- or **R<sup>17</sup>** and **R<sup>18</sup>** when taken together form an optionally substituted carbocyclic ring of 3-7 atoms or optionally substituted heterocyclyl;
- R<sup>19</sup>** is selected from: hydrogen, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl, optionally substituted C<sub>3-7</sub>cycloalkyl, optionally substituted heterocyclyl or optionally substituted heterocyclylC<sub>1-6</sub>alkyl;
- B** is selected from optionally substituted C<sub>1-6</sub>alkylene or the group  forms an optionally substituted C<sub>4-7</sub>heterocyclic ring, wherein the optional substituents are selected from **R<sup>12</sup>**, **R<sup>13</sup>** and **R<sup>14</sup>**;

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the group preferably forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms, wherein the optional substituents are selected from  $R^{12}$ ,  $R^{13}$  and  $R^{14}$ ;

- $K$  is selected from: a direct bond,  $-(CH_2)_{s1}-$ ,  $-(CH_2)_{s2}-O-(CH_2)_s-$ ,  $-(CH_2)_{s1}-C(O)-(CH_2)_{s2}-$ ,  
 5  $-(CH_2)_{s1}-S(O_n)-(CH_2)_{s2}-$ ,  $-(CH_2)_{s1}-N(R^{18})-(CH_2)_{s2}-$ ,  $-(CH_2)_{s1}-C(O)N(R^9)-(CH_2)_{s2}-$ ,  
 $-(CH_2)_{s1}-N(R^9)C(O)-(CH_2)_{s2}-$ ,  $-(CH_2)_{s1}-N(R^9)C(O)N(R^9)-(CH_2)_{s2}-$ ,  
 $-(CH_2)_{s1}-OC(O)-(CH_2)_{s2}-$ ,  $-(CH_2)_{s1}-C(O)O-(CH_2)_{s2}-$ ,  $-(CH_2)_{s1}-N(R^9)C(O)O-(CH_2)_{s2}-$ ,  
 $-(CH_2)_{s1}-OC(O)N(R^9)-(CH_2)_{s2}-$ ,  $-(CH_2)_{s1}-OS(O_n)-(CH_2)_{s2}-$ , or  
 $-(CH_2)_{s1}-S(O_n)-O-(CH_2)_{s2}-$ ,  $-(CH_2)_{s1}-S(O)_2N(R^9)-(CH_2)_{s2}-$ ,  
 10  $-(CH_2)_{s1}-N(R^9)S(O)_2-(CH_2)_{s2}-$ ; wherein the  $-(CH_2)_{s1}-$  and  $-(CH_2)_{s2}-$  groups are  
 independently optionally substituted by hydroxy, fluoro, cyano, carbamoyl,  $C_{1-4}$ alkyl  
 and  $C_{1-4}$ alkoxy,

$n$  is an integer from 0 to 2;

$s$  is an integer from 0 to 4;

- 15  $s1$  and  $s2$  are independently selected from an integer from 0 to 4, and

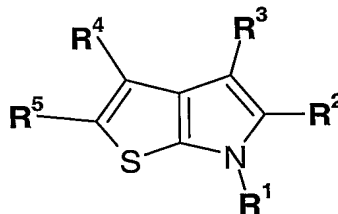
$s1+s2$  is less than or equal to 4;

$cc$  is an integer between 0 to 2

or a salt, pro-drug or solvate thereof.

According to a further aspect of the invention there is provided a compound of Formula

20 (Ic)

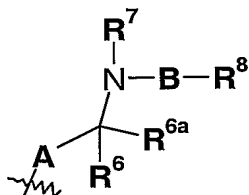


Formula (Ic)

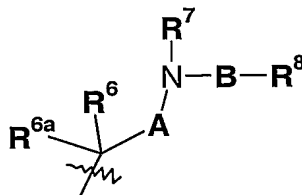
wherein

$R^3$  is selected from a group of Formula (IIa) or Formula (IIb):

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Formula (IIa)



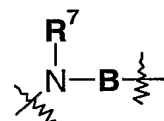
Formula (IIb)

and **R<sup>1</sup>**, **R<sup>2</sup>**, **R<sup>4</sup>**, **R<sup>5</sup>**, **R<sup>6</sup>**, **R<sup>6a</sup>**, **R<sup>7</sup>**, **R<sup>8</sup>**, **A** and **B** are as defined above;  
or salt, solvate or pro-drug thereof.

- 5 A further preferred group of compounds of the invention comprises a compound of Formula (Ic), wherein:

**A** is optionally substituted C<sub>1-5</sub>alkylene;

**B** is selected from optionally substituted C<sub>1-6</sub>alkylene or the group



forms a

ring containing C<sub>5-7</sub>heterocyclic ring;

- 10 **R<sup>1</sup>** is hydrogen or C<sub>1-4</sub>alkyl;

**R<sup>6</sup>** and **R<sup>6a</sup>**, are independently selected from hydrogen and optionally substituted C<sub>1-6</sub>alkyl;

**R<sup>7</sup>** is selected from: hydrogen or C<sub>1-4</sub>alkyl;

**R<sup>8</sup>** is selected from hydrogen, cyano, C<sub>1-6</sub>alkyl, haloC<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkynyl, C<sub>1-6</sub>alkanoyl,

- 15 C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, C<sub>1-6</sub>alkoxycarbonyl, N,N-di-C<sub>1-4</sub>alkylamino, aryl, arylC<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-6</sub>alkyl, heterocyclyl, heterocyclylC<sub>1-6</sub>alkyl, or heterocyclylcarbonylC<sub>1-4</sub>alkyl wherein aryl and heterocyclyl rings are optionally substituted by cyano and C<sub>1-4</sub>alkyl; and

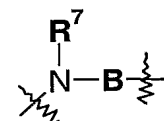
**R<sup>2</sup>**, **R<sup>4</sup>**, and **R<sup>5</sup>**; are as defined above

or salt, solvate or pro-drug thereof.

- 20 A further preferred group of compounds of the invention comprises a compound of Formula (Ic), wherein:

**A** is optionally substituted C<sub>1-5</sub>alkylene;

**B** is selected from optionally substituted C<sub>1-6</sub>alkylene or the group



forms a

ring containing C<sub>5-7</sub>heterocyclic ring;

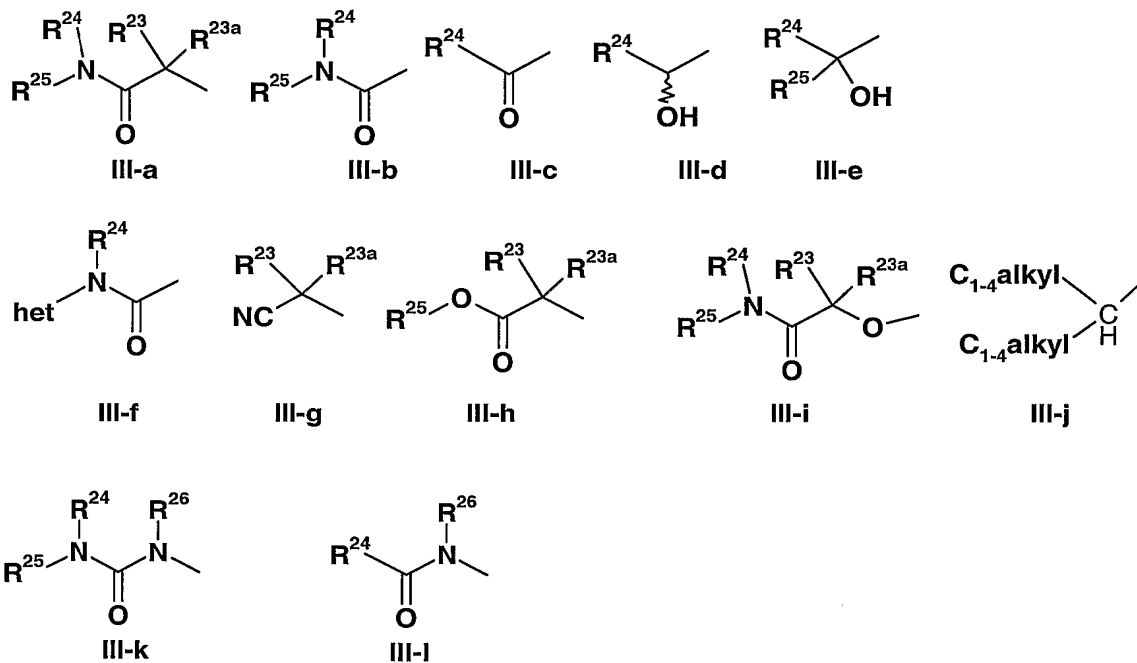
- 25 **R<sup>1</sup>** is hydrogen or C<sub>1-4</sub>alkyl, preferably hydrogen;

**R<sup>2</sup>** is an optionally substituted monocyclic aromatic ring structure, preferably optionally substituted phenyl, most preferably 3,5-dimethylphen-1-yl;

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$R^4$  is hydrogen or  $C_{1-4}$ alkyl, preferably hydrogen;

$R^5$  is a group of Formula (III) wherein the group of Formula (III) is selected from a group of Formula III-a; III-b; III-c; III-d; III-e; III-f, III-g, III-h, III-i, III-j, III-k or III-l



5

wherein  $R^{23}$ ,  $R^{23a}$ ,  $R^{24}$ ,  $R^{25}$  and  $R^{26}$  are as defined above, preferably the group of Formula (III) is selected from (III-a), (III-g) and (III-h);

$R^6$  and  $R^{6a}$ , are independently selected from hydrogen and optionally substituted  $C_{1-6}$ alkyl;

$R^7$  is selected from: hydrogen or  $C_{1-4}$ alkyl;

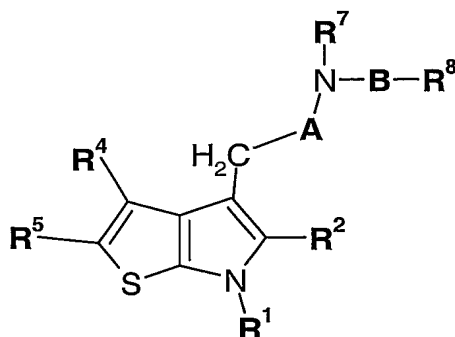
10  $R^8$  is selected from hydrogen, cyano,  $C_{1-6}$ alkyl, halo $C_{1-6}$ alkyl,  $C_{2-6}$ alkynyl,  $C_{1-6}$ alkanoyl,  $C_{1-4}$ alkoxy $C_{1-4}$ alkyl,  $C_{1-6}$ alkoxycarbonyl, N,N-di- $C_{1-4}$ alkylamino, aryl, aryl $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-6}$ alkyl, heterocyclyl, heterocyclyl $C_{1-6}$ alkyl, or heterocyclylcarbonyl $C_{1-4}$ alkyl wherein aryl and heterocyclyl rings are optionally substituted by cyano and  $C_{1-4}$ alkyl; and

15  $R^2$ ,  $R^4$ , and  $R^5$ ; are as defined above

or salt, solvate or pro-drug thereof.

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A further preferred group of compounds of the invention comprises a compound of Formula (Id):

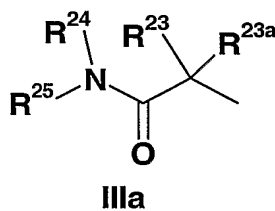


Formula (Id)

- 5      Wherein **R<sup>1</sup>**, **R<sup>2</sup>**, **R<sup>4</sup>**, **R<sup>5</sup>**; **R<sup>7</sup>**, **R<sup>8</sup>**, **A** and **B** are as defined above or salt, solvate or pro-drug thereof.

A yet further preferred group of compounds of the invention comprises a compound of Formula (I), (Ia), (Ib), (Ic) or (Id) wherein:

- 10      **R<sup>5</sup>** is a group of Formula (III) wherein the group of Formula (III) is a group of formula **IIIa**:



IIIa

;

wherein **R<sup>23</sup>**, **R<sup>23a</sup>**, **R<sup>24</sup>** and **R<sup>25</sup>** are as defined above; or a salt, pro-drug or solvate thereof.

- 15      According to a further aspect of the invention there is provided a compound of Formula (I) or (Ia), or salt, solvate or pro-drug thereof, wherein **R<sup>3</sup>** is selected from a group of Formula (IIc) or Formula (IId) and **R<sup>1</sup>**, **R<sup>2</sup>**, **R<sup>4</sup>** and **R<sup>5</sup>** are as defined above.

According to a further aspect of the invention there is provided a compound of Formula (I) or (Ia), or salt, solvate or pro-drug thereof, wherein **R<sup>3</sup>** is selected from a group of Formula (IIe) or Formula (IIf) and **R<sup>1</sup>**, **R<sup>2</sup>**, **R<sup>4</sup>** and **R<sup>5</sup>** are as defined above.

- 20      According to a further aspect of the invention there is provided a compound of Formula (I) or (Ia), or salt, solvate or pro-drug thereof, wherein **R<sup>3</sup>** is selected from a group of Formula (IIa), Formula (IIc) or Formula (IIe) and **R<sup>1</sup>**, **R<sup>2</sup>**, **R<sup>4</sup>** and **R<sup>5</sup>** are as defined above.

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According to a further aspect of the invention there is provided a compound of Formula (I) or (Ia), or salt, solvate or pro-drug thereof, wherein **R**<sup>3</sup> is selected from a group of Formula (IIb), Formula (IIc) or Formula (IIe) and **R**<sup>1</sup>, **R**<sup>2</sup>, **R**<sup>4</sup> and **R**<sup>5</sup> are as defined above.

A preferred group of compounds according to the present invention are wherein the  
5 compound is selected from:

- {(2*S*)-2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]propyl}(2-pyridin-4-ylethyl)amine;
- 2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-{2-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;
- 10 2-[1,1-dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[4-(2-hydroxy-3-{4-acetylpiperazin-1-yl}prop-1-yl)piperazin-1-yl]ethyl-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[(2-{4-{2-hydroxy-3-piperiazin-1-ylprop-1-yl}piperazin-1-yl}ethyl)-5-(3,5-dimethylphenyl)-6*H*-
- 15 thieno[2,3-*b*]pyrrole;
- 2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-[2-(3-pyridin-4-ylpyrrolidin-1-yl)ethyl]-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-[2-(3-pyridin-2-ylpyrrolidin-1-yl)ethyl]-6*H*-thieno[2,3-*b*]pyrrole;
- 20 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-(4-{morpholinocarbonyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-[2-(4-{2,6-dimethylmorpholinocarbonyl}piperidin-1-yl)ethyl]-6*H*-thieno[2,3-*b*]pyrrole;
- 25 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[1-oxo-2-{4-(1,1-dioxidotetrahydrothien-3-yl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[1-oxo-2-{4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-
- 30 6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[1-oxo-2-{4-(morpholinocarbonyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;



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- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[1-oxo-2-{3-methyl-4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 5 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[1-oxo-2-methyl-2-{4-(1,1-dioxidotetrahydro-3-thienyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[1-oxo-3-{4-(1,1-dioxidotetrahydro-3-thienyl)piperazin-1-yl}propyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 10 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-ylmethyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 15 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{4-(6-hydroxypyrid-3-ylmethyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-(4-{(3*aR*,6*aS*)-tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-ylcarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 20 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{4-(morpholinocarbonyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 25 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-(4-{*N,N*-dimethylaminocarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[*N*-isopropylaminocarbonylmethylpiperazin-1-yl]ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 30

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- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[2-(4-{ tetrahydrofuran-2-ylcarbonyl}piperazin-1-yl)ethyl]-5-(3,5-  
dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 5 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{ 4-  
(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-ylmethyl)piperazin-1-  
yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[2-(4-{ piperidin-1-ylcarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-  
dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 10 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[2-(4-{ azetidin-1-ylcarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-  
dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-(4-pyrid-4-ylpiperidin-  
1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 15 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{ 4-(1,1-  
dioxidotetrahydro-3-thienyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-  
6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{ 4-  
(4-acetyl piperazin-1-yl)carbonylpiperidin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-  
20 6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{ 4-  
((3*aR*,6*aS*)-tetrahydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrol-5-ylcarbonyl)piperidin-1-  
yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
25 4-[2-(4-{ morpholinocarbonylmethyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-  
6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[(2-(4-{ tetrahydro-2*H*-  
pyran-4-ylcarbonylamino}piperidin-1-yl)ethyl)-5-(3,5-dimethylphenyl)-  
6*H*-thieno[2,3-*b*]pyrrole;
- 30 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[2-(4-{ morpholinocarbonylamino}piperidin-1-yl)ethyl]-5-(3,5-  
dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;

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- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[2-(4-{3-oxo-3-morpholinoprop-1-yl}piperidin-1-yl)ethyl]-5-(3,5-  
dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 5 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[2-(4-{isopropylsulphonylaminomethyl}piperidin-1-yl)ethyl]-5-(3,5-  
dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[2-(4-{3-hydroxypyrrolidin-1-ylcarbonyl}piperidin-1-yl)ethyl]-5-(3,5-  
dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 10 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[2-(3-oxo-4-{pyrrolidin-1-ylcarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-  
dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[2-(4-{4-oxo-4-pyrrolidin-1-ylbut-3-yl}piperazin-1-yl)ethyl]-5-(3,5-  
15 dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[2-(4-{3-oxo-3-pyrrolidin-1-ylprop-2-yl}piperazin-1-yl)ethyl]-5-(3,5-  
dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[2-(4-{pyrrolidin-1-ylcarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-  
20 dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[2-(4-methoxy-4-{N,N-diethylaminomethyl}piperidin-1-yl)ethyl]-5-(3,5-  
dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 25 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
4-[4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-ylmethyl]-5-(3,5-dimethylphenyl)-  
6*H*-thieno[2,3-*b*]pyrrole; and
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[4-  
(morpholinocarbonyl)piperidin-1-ylmethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-  
30 *b*]pyrrole;
- or a salt, pro-drug or solvate thereof.

A further preferred group of compounds according to the present invention are wherein the compound is selected from:

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- { (2*S*)-2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]propyl}(2-pyridin-4-ylethyl)amine;  
 2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-  
 { 2-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]ethyl }-6*H*-thieno[2,3-*b*]pyrrole;  
 5 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
 4-[2-(4-{ morpholinocarbonyl }piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-  
 thieno[2,3-*b*]pyrrole;  
 2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-[2-  
 (4-{ 2,6-dimethylmorpholinocarbonyl }piperidin-1-yl)ethyl]-6*H*-thieno[2,3-*b*]pyrrole;  
 10 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[1-oxo-2-{ 4-(1,1-  
 dioxidotetrahydrothien-3-yl)piperazin-1-yl }ethyl]-5-(3,5-dimethylphenyl)-  
 6*H*-thieno[2,3-*b*]pyrrole;  
 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[1-oxo-2-methyl-2-{ 4-  
 (1,1-dioxidotetrahydro-3-thienyl)piperazin-1-yl }ethyl]-5-(3,5-dimethylphenyl)-  
 15 6*H*-thieno[2,3-*b*]pyrrole;  
 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{ 4-  
 (pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl }ethyl]-5-(3,5-dimethylphenyl)-6*H*-  
 thieno[2,3-*b*]pyrrole;  
 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{ 4-  
 (2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-ylmethyl)piperazin-1-yl }ethyl]-5-(3,5-  
 20 dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;  
 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{ 4-  
 (morpholinocarbonyl)piperazin-1-yl }ethyl]-5-(3,5-dimethylphenyl)-  
 6*H*-thieno[2,3-*b*]pyrrole;  
 25 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
 4-[2-(4-{ *N,N*-dimethylaminocarbonylmethyl }piperazin-1-yl)ethyl]-5-(3,5-  
 dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;  
 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
 4-[*N*-isopropylaminocarbonylmethyl)piperazin-1-yl }ethyl]-5-(3,5-  
 30 dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;  
 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{ 4-  
 (1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-ylmethyl)piperazin-1-  
 yl }ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;

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- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
 4-[2-(4-{azetidin-1-ylcarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-  
 dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-(4-pyrid-4-ylpiperidin-  
 5 1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[2-(1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl)]-4-[2-{4-  
 ((3*aR*,6*aS*)-tetrahydro-3*aH*-[1,3]dioxolo[4,5-*c*]pyrrol-5-ylcarbonyl)piperidin-1-  
 yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
 10 4-[2-(4-{3-hydroxypyrrolidin-1-ylcarbonyl}piperidin-1-yl)ethyl]-5-(3,5-  
 dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
 4-[2-(4-{3-oxo-3-pyrrolidin-1-ylprop-2-yl}piperazin-1-yl)ethyl]-5-(3,5-  
 dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole; and
- 15 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
 4-[2-(4-{pyrrolidin-1-ylcarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-  
 dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole; and
- or a salt, pro-drug or solvate thereof.

A most preferred group of compounds according to the present invention are wherein  
 20 the compound is selected from:

- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-  
 4-[2-(4-{morpholinocarbonyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-  
 thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[1-oxo-2-methyl-2-{4-  
 25 (1,1-dioxidotetrahydro-3-thienyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-  
 6*H*-thieno[2,3-*b*]pyrrole;
- 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-4-[2-{4-  
 (pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-  
 thieno[2,3-*b*]pyrrole;
- 30 2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-ylethyl)]-4-[2-{4-  
 (2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-ylmethyl)piperazin-1-yl}ethyl]-5-(3,5-  
 dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;

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2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-

4-[2-(4-{3-hydroxypyrrolidin-1-ylcarbonyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole; and

2-[1,1-Dimethyl-2-oxo-2-(azabicyclo[2.2.1]heptan-7-yl)ethyl]-

5 4-[2-(4-{3-oxo-3-pyrrolidin-1-ylprop-2-yl}piperazin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;

or a salt, pro-drug or solvate thereof.

In another embodiment of the invention a particularly preferred group of compounds according to the present invention are wherein the compound is selected from:

10 *N*-{2-[2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylbutan-1-amine;

*N*-{2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylbutan-1-amine;

*N*-{2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-

15 dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylethyl-1-amine;

{(2*S*)-2-[2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]propyl}(2-pyridin-4-ylethyl)amine;

*N*-{2-[2-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-

dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylbutan-1-amine;

20 *N*-{2-[2-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]ethyl}-4-pyridin-4-ylethyl-1-amine;

{(2*S*)-2-[2-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrol-4-yl]propyl}(2-pyridin-4-ylethyl)amine;

2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-{2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

25 2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-{2-[4-(pyridin-2-ylmethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-{2-[4-methylpiperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

30 2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-{2-[4-(pyridin-4-yl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

2-[2-(2-azabicyclo[2.2.2]oct-2-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-[2-(4-methylpiperazin-1-yl)ethyl]-6*H*-thieno[2,3-*b*]pyrrole;

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4-[2-(4-allylpiperazin-1-yl)ethyl]-2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;

2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-{2-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

5 and

2-[2-(7-azabicyclo[2.2.1]hept-7-yl)-1,1-dimethyl-2-oxoethyl]-5-(3,5-dimethylphenyl)-4-{2-[4-(pyridin-4-ylmethyl)piperazin-1-yl]ethyl}-6*H*-thieno[2,3-*b*]pyrrole;

or a salt, pro-drug or solvate thereof.

The compounds of Formula (I) may be administered in the form of a pro-drug which is  
 10 broken down in the human or animal body to give a compound of the Formula (I). Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the Formula (I). Various forms of pro-drugs are known in the art. For examples of such pro-drug derivatives, see:

- a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in  
 15 Enzymology, Vol. 42, p. 309-396, edited by K. Widder, et al. (Academic Press, 1985);
- b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);
- 20 c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);
- d) H. Bundgaard, et al., Journal of Pharmaceutical Sciences, 77, 285 (1988); and
- e) N. Kakeya, et al., Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of the Formula (I) containing a carboxy or a hydroxy group is, for example, a pharmaceutically-acceptable ester which is  
 25 hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically-acceptable esters for carboxy include C<sub>1-6</sub>alkoxymethyl esters for example methoxymethyl, C<sub>1-6</sub>alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C<sub>3-8</sub>cycloalkoxycarbonyloxyC<sub>1-6</sub>alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters, for example 5-methyl-1,3-  
 30 dioxolen-2-onylmethyl; and C<sub>1-6</sub>alkoxycarbonyloxyethyl esters.

An in-vivo hydrolysable ester of a compound of the Formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and  $\alpha$ -acyloxyalkyl ethers and related compounds which as a result of the in-

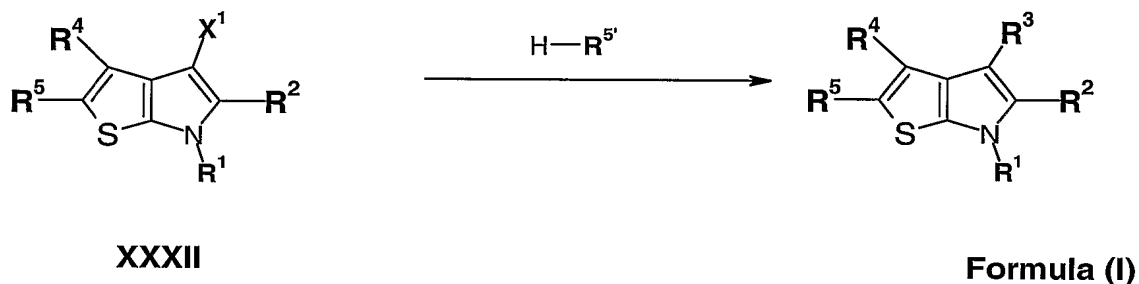
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vivo hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of  $\alpha$ -acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of in-vivo hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give  
 5 alkyl carbonate esters), dialkylcarbamoyl and N-(dialkylaminoethyl)-N-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

A suitable pharmaceutically-acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example  
 10 hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically-acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with  
 15 methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of Formula (I) can be prepared by a process comprising a step selected from (a) to (i) as follows, these processes are provided as a further feature of the invention:-

(a) Reaction of a compound of formula XXXII with a compound of formula  $H-R^{5'}$  to form  
 20 a compound of Formula (I),



wherein  $X^1$  is selected from:

and

;  $L^1$  is a displaceable group;

$H-R^{5'}$  is selected from:

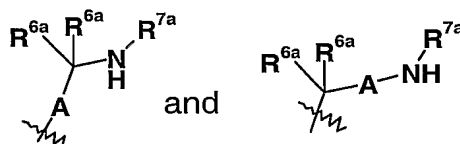
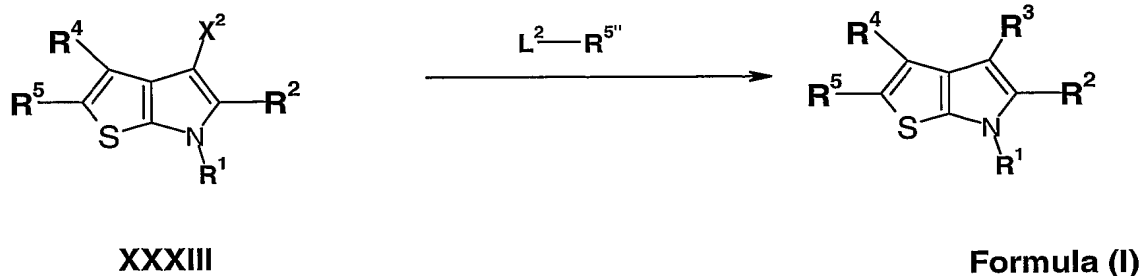
,
and

;

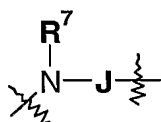


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- (b) Reaction of a compound of formula XXXIII with a compound of formula  $L^2-R^{5''}$  to form a compound of Formula (I),



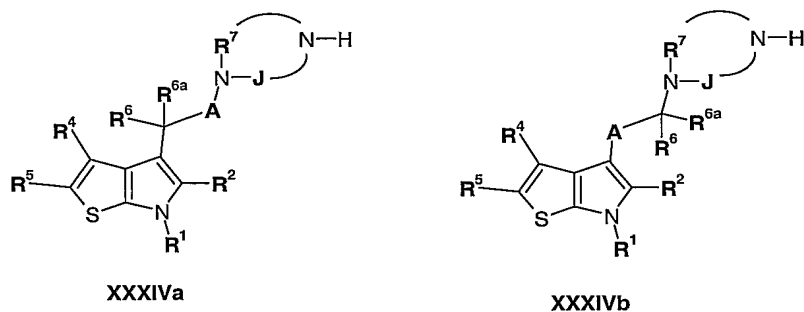
- wherein  $X^2$  is selected from: ;  $L^2$  is a displaceable group and  $R^{7a}$  is selected from the definition of  $R^7$  or  $R^{22}$  above, and
- $L^2-R^{5''}$  is selected from:  $L^2-B-R^8$ ,  $L^2-J-K-R^8$  and  $L^2-R^{21}$ ;
- (c) For compounds of Formula (I) wherein  $R^3$  is a group of Formula (IIa), (IIb), (IIc) or (IId) and  $R^7$  is other than part of a heterocyclic ring or hydrogen, reaction of a compound of Formula (I) wherein  $R^3$  is a group of Formula (IIa), (IIb), (IIc) or (IId) and  $R^7$  is hydrogen with a group of formula  $L^3-R^{7a}$ , wherein  $R^{7a}$  is as defined above for  $R^7$  with the exclusion of hydrogen and  $L^3$  is a displaceable group;
- (d) For compounds of Formula (I) wherein  $R^3$  is a group of Formula (IIe) or (IIf) and  $R^{21}$  is other than hydrogen, reaction of a compound of Formula (I) wherein  $R^3$  is a group of Formula (IIe) or (IIf) and  $R^{21}$  is hydrogen with a group of formula  $L^4-R^{21a}$ , wherein  $R^{21a}$  is as defined above for  $R^{21}$  with the exclusion of hydrogen and  $L^4$  is a displaceable group;
- (e) For compounds of Formula (I) wherein  $R^3$  is a group of Formula (IIe) or (IIf) and  $R^{22}$  is other than hydrogen, reaction of a compound of Formula (I) wherein  $R^3$  is a group of Formula (IIe) or (IIf) and  $R^{22}$  is hydrogen with a group of formula  $L^5-R^{22a}$ , wherein  $R^{22a}$  is as defined above for  $R^{22}$  with the exclusion of hydrogen and  $L^5$  is a displaceable group;
- (f) For compounds of Formula (I) wherein  $R^3$  is a group of Formula (IIc) or (IId) and



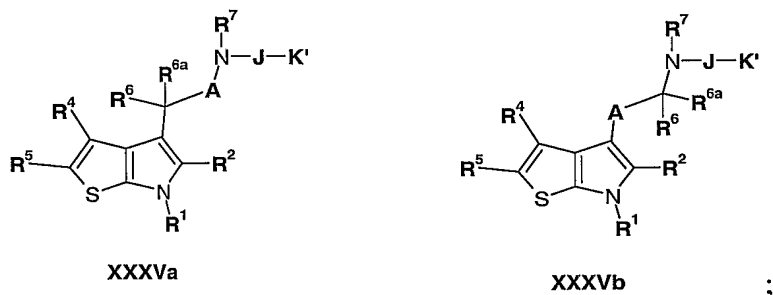
the group together forms an optionally substituted nitrogen-containing heterocyclic ring containing 4-7 carbons atoms, reaction of a compound of Formula

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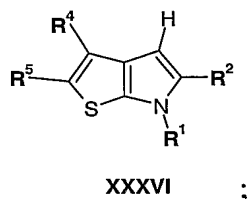
**XXXIVa** or **XXXIVb**, with a compound of Formula  $L^6-K-R^8$ , wherein  $L^6$  is a displaceable group



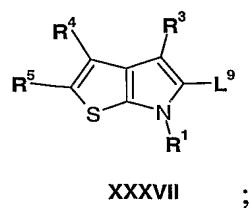
- (g) For compounds of Formula (I) wherein  $R^3$  is a group of Formula (IIc) or (IId), reaction of  
 5 a compound of Formula **XXXVa** or **XXXVb**, with a compound of Formula  $L^7-K''-R^8$ , wherein  $L^7$  is a displaceable group, and wherein the groups  $K'$  and  $K''$  comprise groups which when reacted together form  $K$ ,



- (h) reaction of a compound of Formula **XXXVI** with an electrophilic compound of the  
 10 formula  $L^8-R^5$ , wherein  $L^8$  is a displaceable group



- (i) reaction of a compound of Formula **XXXVII** with a compound of the formula  $L^{10}-R^2$ , wherein  $L^9$  is a leaving group and  $L^{10}$  is an activating group or  $L^9$  is an activating group and  $L^{10}$  is a leaving group



and thereafter if necessary:

- i) converting a compound of the Formula (I) into another compound of the Formula (I);

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- ii) removing any protecting groups;
- iii) forming a salt, pro-drug or solvate.

Specific reaction conditions for the above reactions are as follows:

*Process a)* Compounds of formula **XXXII** and  $H-R^{5'}$  can be coupled together in the presence of an organic base (such as DIPEA [di-isopropylethylamine]) or an inorganic base (such as potassium carbonate) base, in a suitable solvent such as DMA or DMF, at a temperature from room temperature and 120°C. Suitable displaceable groups include: a halide, such as chloro, or a methane sulphonate or toluene sulphonate;

*Process b)* Compounds of **XXXIII** and  $L^2-R^{5''}$  can be coupled together in the presence of an organic base (such as DIPEA) or an inorganic base (such as potassium carbonate), in a suitable solvent such as DMA or DMF, at a temperature from room temperature to 120°C. Suitable displaceable groups include: a halide, such as chloro, or a methane sulphonate or toluene sulphonate,

alternatively if  $L^2$  is a hydroxy group then the  $L^2-R^{5''}$  can be reacted with a compound of formula **XXXIII** under Mitsunobu reaction conditions;

*Process c, d, e and f)* Reaction conditions to facilitate these reactions can be using

(i) alkylation reaction conditions or (ii) acylation reaction conditions: Examples of said conditions include:

(i) alkylation reaction conditions - the presence of an organic base (such as DIPEA) or an inorganic base (such as potassium carbonate), in a suitable solvent such as DMF, DMA, DCM, at a temperature from room temperature to 120°C. Suitable displaceable groups include: a halide, such as chloro, methane sulphonate or toluene sulphonate;

(ii) acylation reaction conditions - presence of organic base, such as triethylamine, temperature 0°C to 50-60°C in a suitable solvent such as DCM. Suitable displaceable groups include an acylchloride or an acid anhydride,

*Process g)* The skilled man would be familiar with a variety of reaction conditions and values for  $K'$  and  $K''$ , which when reacted together would form the group **K**, examples of said conditions and values for  $K'$  and  $K''$  include:

(i) For compounds of Formula (I) where  $K$  is  $-(CH_2)_{s1}-N(R^9)C(O)-(CH_2)_{s2}-$  these can be prepared by reacting a compound where  $K'$  is  $-(CH_2)_{s1}-N(R^9)H$  with a carboxylic acid for formula  $HOOC-(CH_2)_{s2}-R^8$  to form the amide. Coupling of amino groups with carboxylic acids are well known in the art and can be facilitated by a number of chemical reactions using an appropriate coupling

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reagent. For example a carbodiimide coupling reaction can be performed with EDCI in the presence of DMAP in a suitable solvent such as DCM, chloroform or DMF at room temperature;

- 5 (ii) *For compounds of Formula (I) where K is  $-(CH_2)_{s1}-C(O)N(R^9)-(CH_2)_{s2}-$  these can be prepared by reacting a compound where  $K'$  is  $-(CH_2)_{s1}-COOH$  with an amine of the  $HN(R^9)-(CH_2)_{s2}-R^8$  to form the amide. Methodology is identical to processes described in (i) above in this section;*
- 10 (iii) *For compounds of Formula (I) where K is  $-(CH_2)_{s1}-N(R^9)C(O)O-(CH_2)_{s2}-$  these can be prepared by reacting a compound where  $K'$  is  $-(CH_2)_{s1}-N(R^9)H$  with a chloroformate of formula  $ClC(O)O-(CH_2)_{s2}-R^8$  in a suitable solvent, such as DCM or chloroform, in the presence of a base, such as *N*-methylmorpholine, pyridine or triethylamine, at a temperature between  $-10^\circ C$  and  $0^\circ C$ ;*
- 15 (iv) *For compounds of Formula (I) where K is  $-(CH_2)_{s1}-OC(O)N(R^9)-(CH_2)_{s2}-$  these can be prepared by reacting a compound where  $K'$  is  $-(CH_2)_{s1}-OC(O)Cl$  with a compound of formula  $HN(R^9)-(CH_2)_{s2}-R^8$ . Methodology is identical to processes described in (iii) above in this section;*
- 20 (v) *For compounds of Formula (I) where K is  $-(CH_2)_{s1}-N(R^9)S(O_2)-(CH_2)_{s2}-$  these can be prepared by reacting a compound where  $K'$  is  $-(CH_2)_{s1}-N(R^9)H$  with a sulphonyl chloride of formula  $ClS(O_2)-(CH_2)_{s2}-R^8$  in the presence of a base, such as triethylamine or pyridine, in a suitable solvent such as chloroform or DCM at a temperature between  $0^\circ C$  and room temperature;*
- 25 (vi) *For compounds of Formula (I) where K is  $-(CH_2)_{s1}-S(O_2)N(R^9)-(CH_2)_{s2}-$  these can be prepared by reacting a compound where  $K'$  is  $-(CH_2)_{s1}-S(O_2)Cl$  with a compound of  $HN(R^9)-(CH_2)_{s2}-R^8$ . Methodology is identical to processes described in (v) above in this section*
- 30 (vii) *For compounds of Formula (I) where K is  $-(CH_2)_{s1}-N(R^9)-(CH_2)_{s2}-$  these can be prepared by reacting a compound where  $K'$  is  $-(CH_2)_{s1}-L^{11}$  with a compound of formula  $HN(R^9)-(CH_2)_{s2}-R^8$ , wherein  $L^{11}$  is a displaceable group. This reaction can be performed in the presence of an organic base (such as DIPEA) or an inorganic base (such as potassium carbonate), in a suitable solvent such as DMA or DMF, at a temperature from room temperature to  $120^\circ C$ . Suitable displaceable groups include: a halide, such as chloro, or a methane sulphonate or toluene sulphonate. Compounds can also be prepared by reacting a compound*

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wherein  $K'$  is  $-(CH_2)_{s1}-N(R^9)H$  with a compound of formula  $L^{11}-(CH_2)_{s2}-R^8$ , under identical conditions.

(viii) *For compounds of Formula (I) where K is  $-(CH_2)_{s1}-O-(CH_2)_{s2}-$*

5 these can be prepared by reacting a compound where  $K'$  is  $-(CH_2)_{s1}-OH$  with a compound of formula  $L^{12}-(CH_2)_{s2}-R^8$ , wherein  $L^{12}$  is a displaceable group. This reaction can be performed in the presence of an organic base (such as potassium *t*-butoxide) or an inorganic base (such as sodium hydride), in a suitable solvent such as DMA or DMF, at a temperature from room temperature to 120°C. Suitable displaceable groups include: a halide, such as bromo, or a methane  
10 sulphonate or toluene sulphonate. Compounds can also be prepared by reacting a compound wherein  $K'$  is  $-(CH_2)_{s1}-L^{12}$  with a compound of formula  $HO-(CH_2)_{s2}-R^8$ , under identical conditions.

(ix) *For compounds of Formula (I) where K is  $-(CH_2)_{s1}-C(O)-(CH_2)_{s2}-$*

15 these can be prepared by reacting a compound where  $K'$  is  $-(CH_2)_{s1}-C(O)-L^{13}$  with a Grignard reagent of formula  $BrMg(CH_2)_{s2}-R^8$ , wherein  $L^{13}$  is a displaceable group. This reaction can be performed in a non-polar solvent such as THF or diethylether at a temperature between room temperature and the boiling point of the solvent. Suitable displaceable groups include: a halide, such as chloro, or an alkoxide. Compounds can also be prepared by reacting a compound  
20 wherein  $K'$  is  $-(CH_2)_{s1}-MgBr$  with a compound of formula  $L^{13}-C(O)-(CH_2)_{s2}-R^8$ , under identical conditions.

*Process h)* reaction of a compound of Formula XXXVI with a compound of the formula  $L^8-R^5$ , can be performed under Friedel Craft conditions, for example in the presence of diethylaluminium chloride in a suitable solvent, such as DCM, in an inert atmosphere such as  
25 nitrogen, at a temperature between room temperature and the boiling point of the solvent or under Mannich conditions, for example, formaldehyde and a primary or secondary amine in acetic acid, in an inert atmosphere such as nitrogen at a temperature between room temperature and 100°C.

*Process i)* reaction of a compound of Formula XXXVII with a compound of the formula  
30  $L^{10}-R^2$ , wherein  $L^9$  is a leaving group and  $L^{10}$  is an activating group or  $L^9$  is an activating group and  $L^{10}$  is a leaving group, can be performed in an aprotic, polar solvent such as THF, using palladium chemistry under Suzuki or Stille conditions, at a temperature between 0 to 70°C.

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It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of Formula (I) may involve, at an appropriate stage, the  
5 addition and subsequent removal of one or more protecting groups.

The protection and de-protection of functional groups is described in 'Protective Groups in Organic Chemistry', edited by J.W.F. McOmie, Plenum Press (1973) and 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991).

10 A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *tert*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The de-protection conditions for the above protecting groups necessarily vary with the choice of  
15 protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *tert*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an  
20 arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

25 A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The de-protection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with  
30 a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

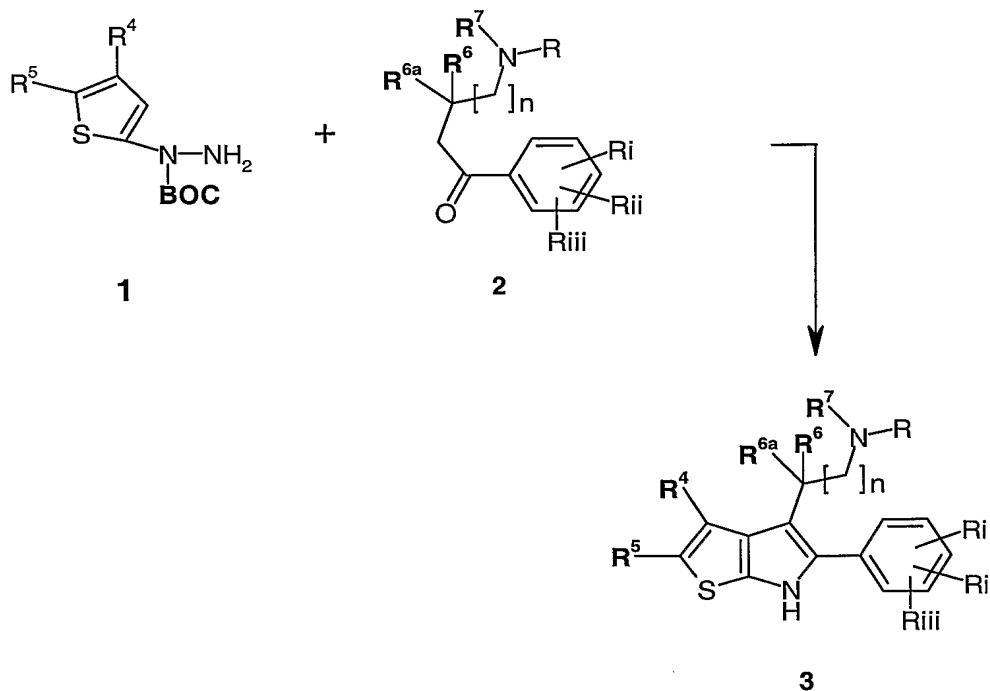
- 54 -

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *tert*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

## EXPERIMENTAL

### GENERAL REACTION SCHEMES

In the following schemes wherein Ri, Rii and Riii represent optional substituents on the phenyl ring which are optionally protected as necessary and R represents a protecting group, group **C** has been depicted as substituted phenyl for illustration purposes only. Other definitions of **C** are also appropriate.

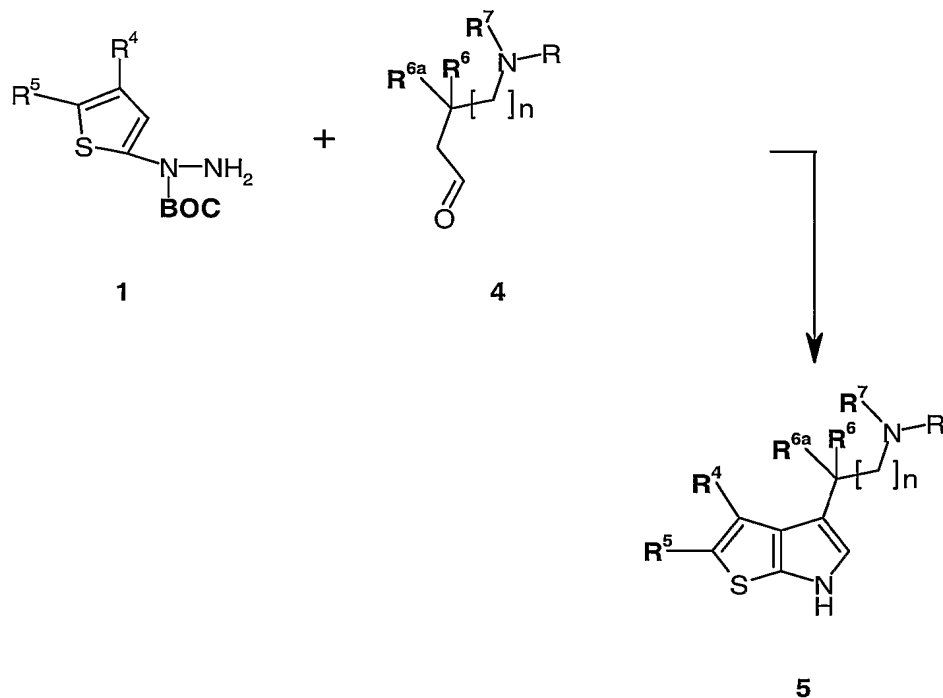


Scheme a

Thienopyrroles, such as **3** can be synthesised by the classic Fisher thienopyrrole synthesis reaction by the condensation of a hydrazine-HCl **1** and a ketone **2**, bearing hydrogen atoms  $\alpha$  to the carbonyl (Scheme a). Treatment of these reactants in a suitable solvent, such as acetic acid, ethanol, *sec*-butanol, toluene, in the presence of an acid, such as sulphuric, hydrochloric, polyphosphoric and/or a Lewis acid, for example, boron trifluoride, zinc

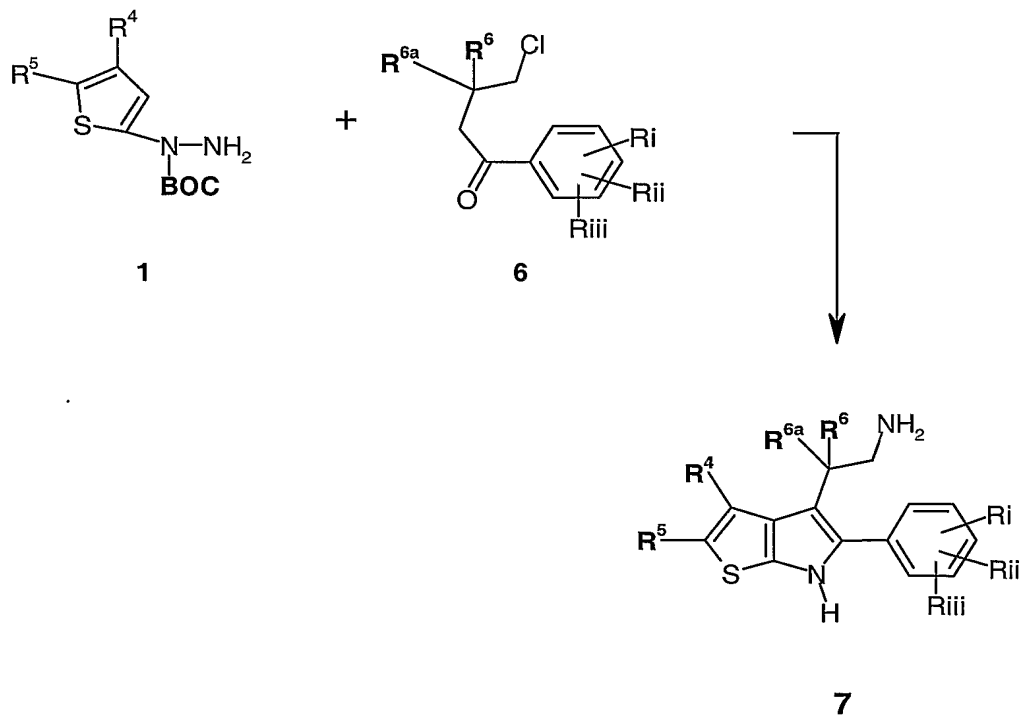
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chloride, magnesium bromide, at elevated temperatures (for example 100 °C), gives the desired product. R represents a protecting group, eg *tert*-butylcarbamate or phthalimide.



Scheme b

- 5 Thienopyrroles, such as represented in structure **5**, can also be made using aldehydes **4**, bearing hydrogen atoms  $\alpha$  to the carbonyl, by cyclization using the conditions above. In this case the substituent at the 2-position must be added later (see scheme d).

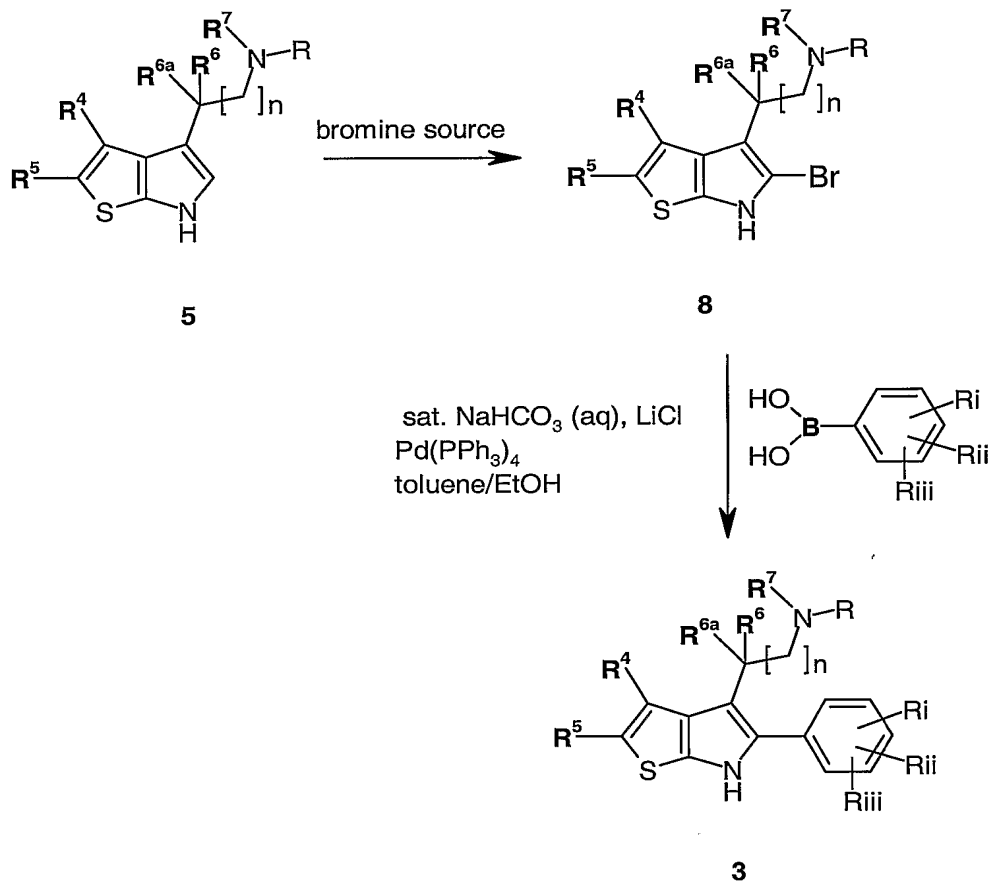




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## Scheme c

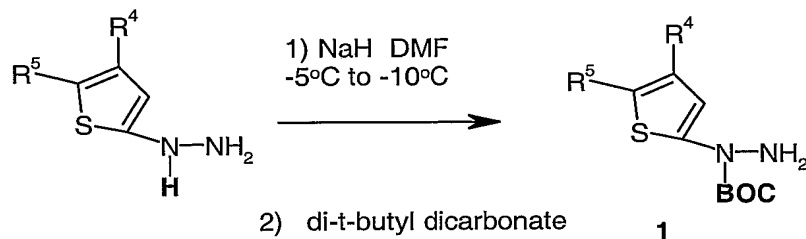
Thienopyrrole may also be synthesised utilising the Granburg reaction, wherein a hydrazine **1** is mixed with ketone **6**, bearing a chlorine atom  $\gamma$  to the carbonyl, and heated in a suitable solvent such as ethanol, *sec*-butanol, toluene at a temperature between 50 °C and 120 °C (Scheme c).



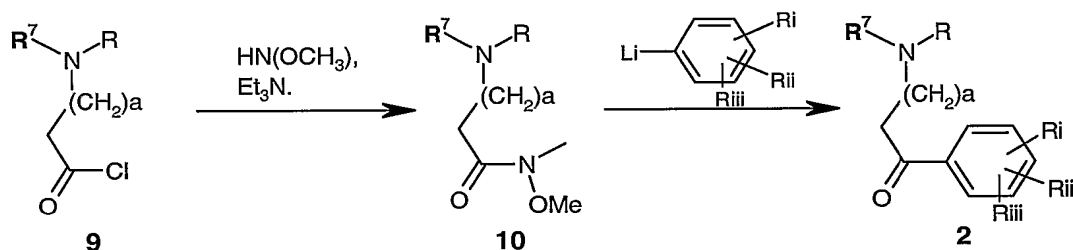
## Scheme d

The thienopyrrole **5** can be treated with a 'bromine source', such as molecular bromide, pyridinium tribromide, pyrrolidone hydrobromide or polymer supported reagent  
 10 equivalents, in an inert solvent such as chloroform, methylene chloride at -10 °C to 25 °C to yield the 2-bromo compound **8** (Scheme d). Reaction under Suzuki conditions with a palladium(0) catalyst, a weak base such as aqueous sodium carbonate or saturated sodium hydrogen carbonate and the like, and a substituted aryl boronic acid from commercial sources or prepared (as described in: Gronowitz, S.; Hornfeldt, A.-B.; Yang, Y.-H *Chem. Sci.* **1986**,  
 15 26, 311-314), in an inert solvent such as toluene, benzene, dioxane, THF, DMF and the like, with heating between 25 °C and 100 °C, preferably 80 °C, for a period of 1-12 hours, to give the desired compound **3**.

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The thiophene **1** can be synthesised by reaction of a hydrazine under the preferred conditions of sodium hydride in DMF at a temperature between -10 °C and -5 °C, followed by reaction with di-*tert*-butyldicarbonate in THF under reflux.

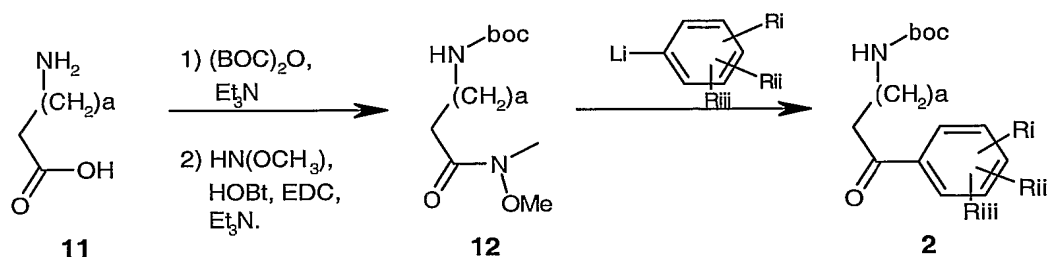


5

Scheme e.

Substituted ketones **2** can be prepared, as outlined in Scheme e starting from appropriate acid chlorides such as **9**. Treatment of the acid chloride with *N,N*-dimethylhydroxylamine hydrochloride in the presence of an amine base such as triethylamine, and a suitable solvent such as methylene chloride at a temperature of -10 °C to 25 °C, yields the amide **10**. Further reaction with a substituted aryl organolithium (prepared essentially as described in Wakefield B, J.; *Organolithium Methods* Academic Press Limited, **1988**, pp. 27-29 and references therein) in an inert solvent such as tetrahydrofuran, diethyl ether, benzene, toluene or mixture thereof and the like, at a temperature between -100 °C and 0 °C then quenching of the reaction mixture with a mineral acid such as hydrochloric acid, yields the aryl ketone **2**.

15



Scheme f.

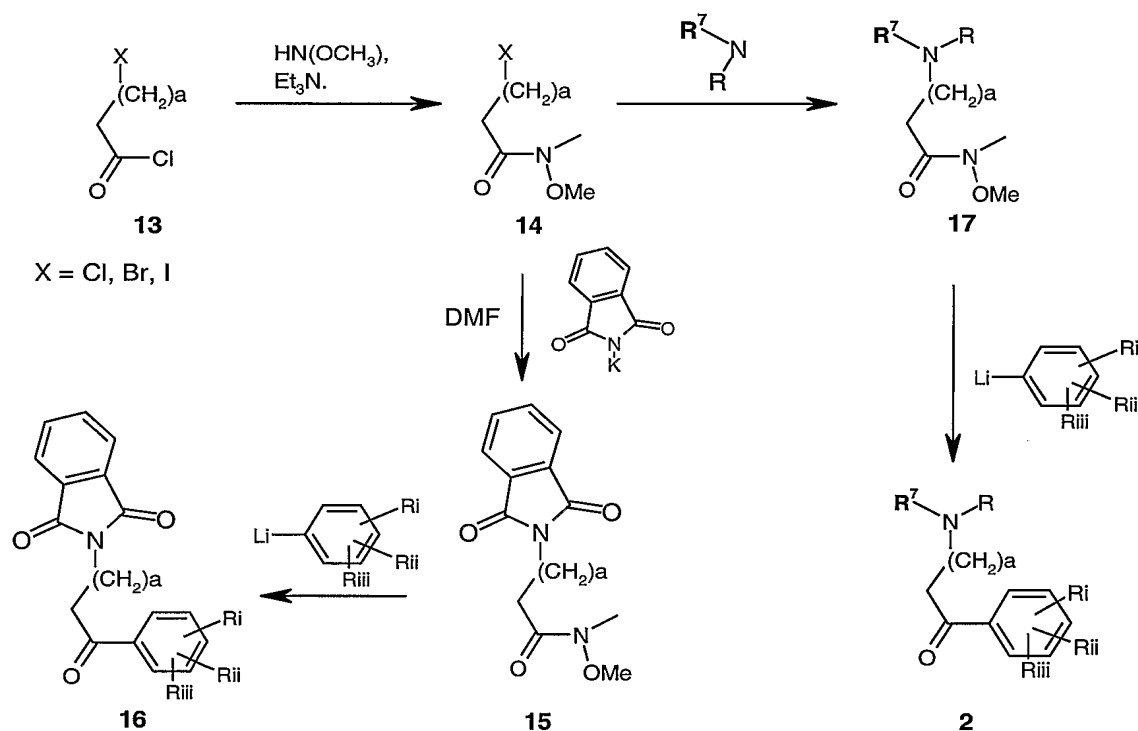
Commencing with a readily available amino acid with a suitable chain length [a] **11**, the nitrogen atom can be brought in at the beginning of the synthesis by the route shown in

20

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Scheme f. Protection of the amine group of **11** with a *tert*-butylcarbamate group is achieved by condensation with di-*tert*-butyl di-carbonate in the presence of an amine base, for example triethylamine, in an inert solvent such as methylene chloride, chloroform, benzene, toluene, tetrahydrofuran and mixtures thereof and the like, at a temperature of -10 °C to 25 °C.

- 5 Coupling of the acid product with *N,N*-dimethylhydroxylamine in the presence of a coupling reagent 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) or 1,3-dicyclohexylcarbodiimide (DCC) or the like, with or without 1-hydroxybenzotriazole (HOBt), and suitable amine base, such as triethylamine and the like, in an inert solvent such as methylene chloride, chloroform, dimethylformamide, or mixture thereof, at or near room
- 10 temperature for a period of 3 to 24 hours provided the corresponding coupled product **12**.
- Following the same route described above for scheme e, the aryl group can then be installed.



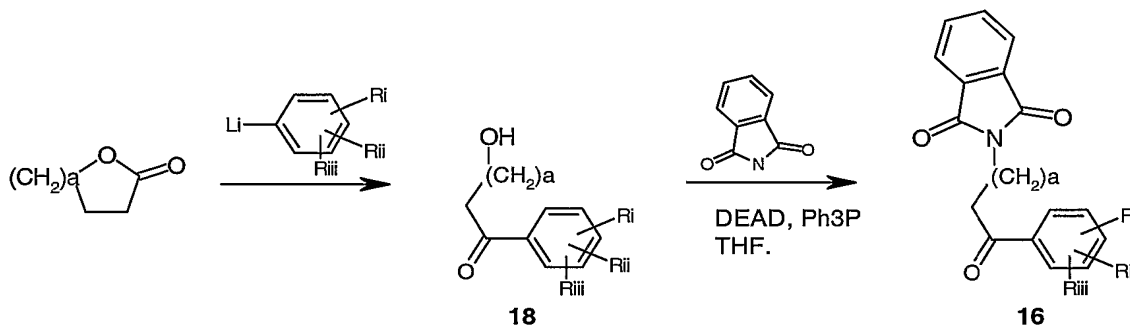
Scheme g.

- Scheme g illustrates another method for the synthesis of ketone such as **2** and **16**,
- 15 where the nitrogen group is introduced at a latter stage. As above a Weinreb amide **14** can be synthesised from an acid chloride. Treatment with the required amine, in an inert solvent such as THF, toluene, water and the such like can displace the group X to give **17**. As above the aryl group can be introduced by displacement of the Weinreb amide with a suitable aryl lithium nucleophile. Alternatively the nitrogen atom can be introduced already protected as a
- 20 phthalimide by displacement of the group X by potassium phthalimide, or similar salt thereof,

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by heating in an inert polar solvent such as DMF, DMSO, THF, toluene with or without the presence of a catalyst such as tetrabutylammonium iodide and the such like, to yield the compound **15**. Again displacement of the Weinreb amide with an organolithium species completes the synthesis of ketone **16** suitable for cyclization under the Fischer condition

5 described above for thienopyrrole synthesis.

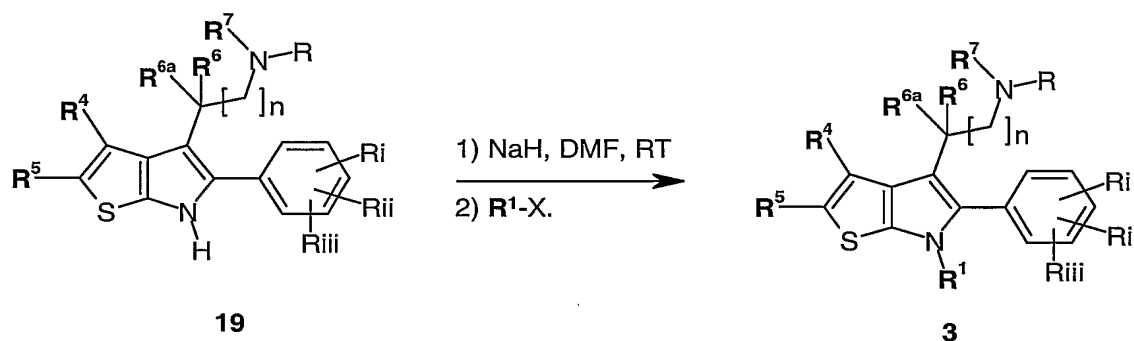


Scheme h.

An alternative approach to a phthalimide protected nitrogen ketone, such as **16**, can be taken by firstly treating a lactone, with an organolithium species as in the above schemes in a

10 suitable solvent such as THF or ether at a low temperature of between  $-100^{\circ}\text{C}$  and  $-50^{\circ}\text{C}$  to yield a primary alcohol **18** (Scheme h). The hydroxyl function of **18** is replaced with a phthalimide group by a Mitsunobu reaction with an activating agent such as diethyldiazocarboxylate (DEAD), diisopropyldiazocarboxylate or the like with triphenylphosphine, tri-butylphosphine and the like, in an inert solvent such as benzene,

15 toluene, tetrahydrofuran or mixtures thereof to give the desired ketone **16**.

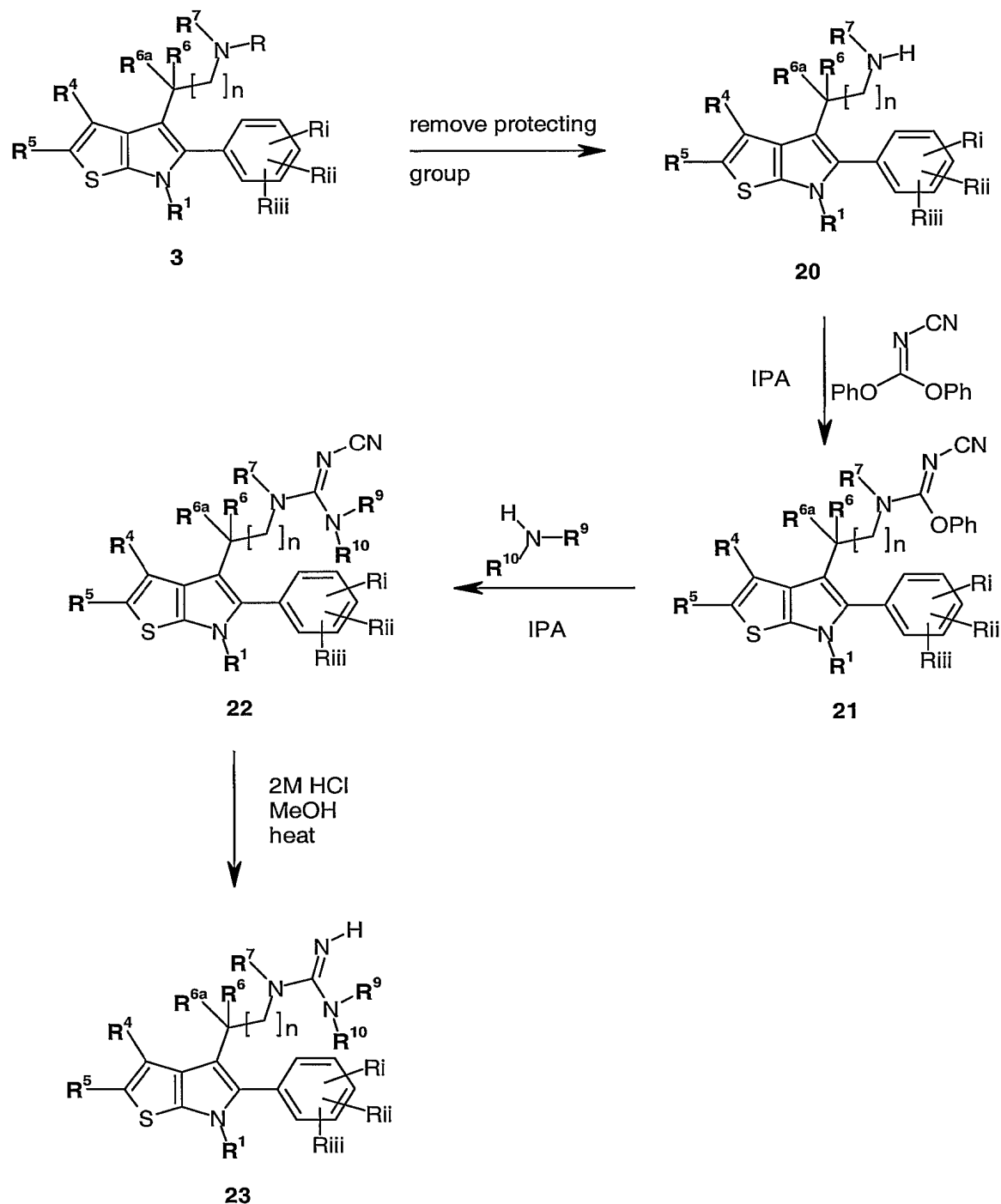


If the group  $\text{R}^1$  was not present on the starting hydrazine before cyclization to form a thienopyrrole it may be added post cyclization by an alkylation reaction (**19**→**3**). The thienopyrrole is de-protonated by a strong base, such as sodium hydride, *n*-butyl lithium,

20 lithium diisopropylamine, sodium hydroxide, potassium *tert*-butoxide in a suitable inert

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solvent such as THF, DMF, DMSO and the such like, and an alkyl halide added and the mixture stirred at room temperature.

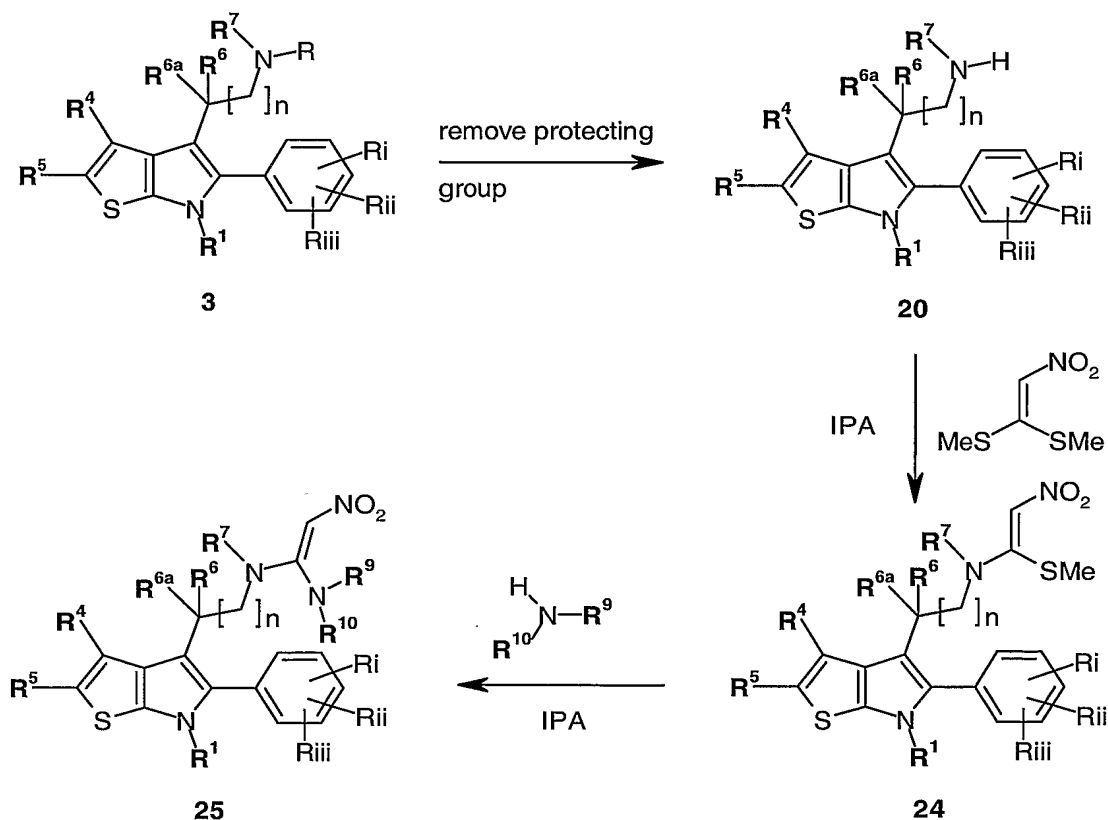


Scheme i

- 5 Depending on the route used above a thienopyrrole **20** suitable for conversion to a cyano-guanidine can be formed by removal of the protecting group, for example if a *tert*-butylcarbamate group was used then removal is accomplished using a strong acid, for

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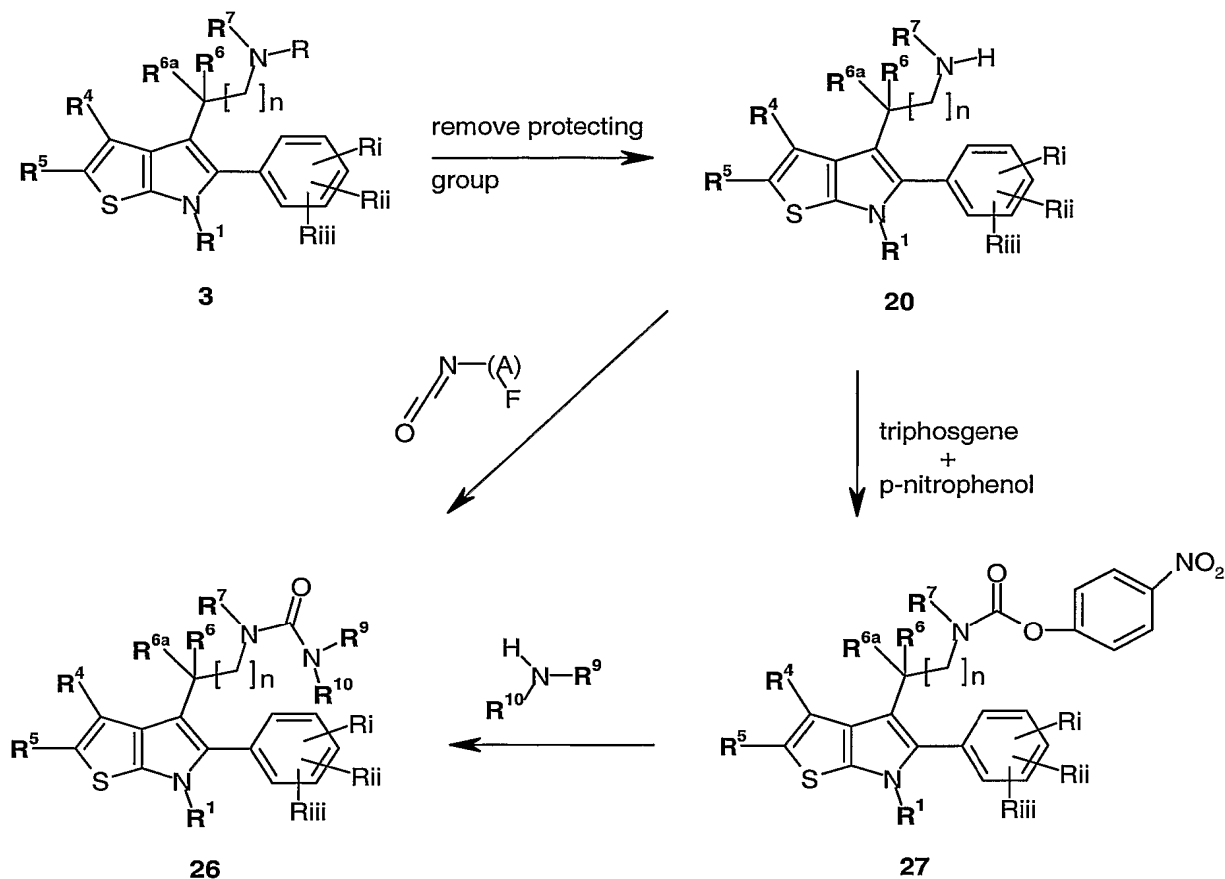
example trifluoroacetic acid or hydrochloric acid in an inert solvent such as methylene chloride, chloroform, THF or dioxane at a temperature between  $-20^{\circ}\text{C}$  and  $25^{\circ}\text{C}$ . A phthalimide group, for example, can be removed by hydrazine in a suitable solvent for example methanol, ethanol, methylene chloride, chloroform, THF dioxane at a temperature between  $-20^{\circ}\text{C}$  and  $25^{\circ}\text{C}$ . The primary amine **20** can be converted to a cyano-guanidine **22** by the two step process of reaction with diphenyl cyanocarbonimide in an inert organic solvent such as *iso*-propyl alcohol, methylene chloride, chloroform, benzene, tetrahydrofuran and the like, at a temperature between  $-20^{\circ}\text{C}$  and  $50^{\circ}\text{C}$ , followed by condensation with an appropriately substituted amine in an inert organic from the list above, with heating at a temperature between  $-20^{\circ}\text{C}$  and  $100^{\circ}\text{C}$  (Scheme i **20**→**21**→**22**). Further treatment of **22** with 2 molar Hydrochloric acid in methanol at elevated temperature yields guanidine compounds **23**.



Scheme j.

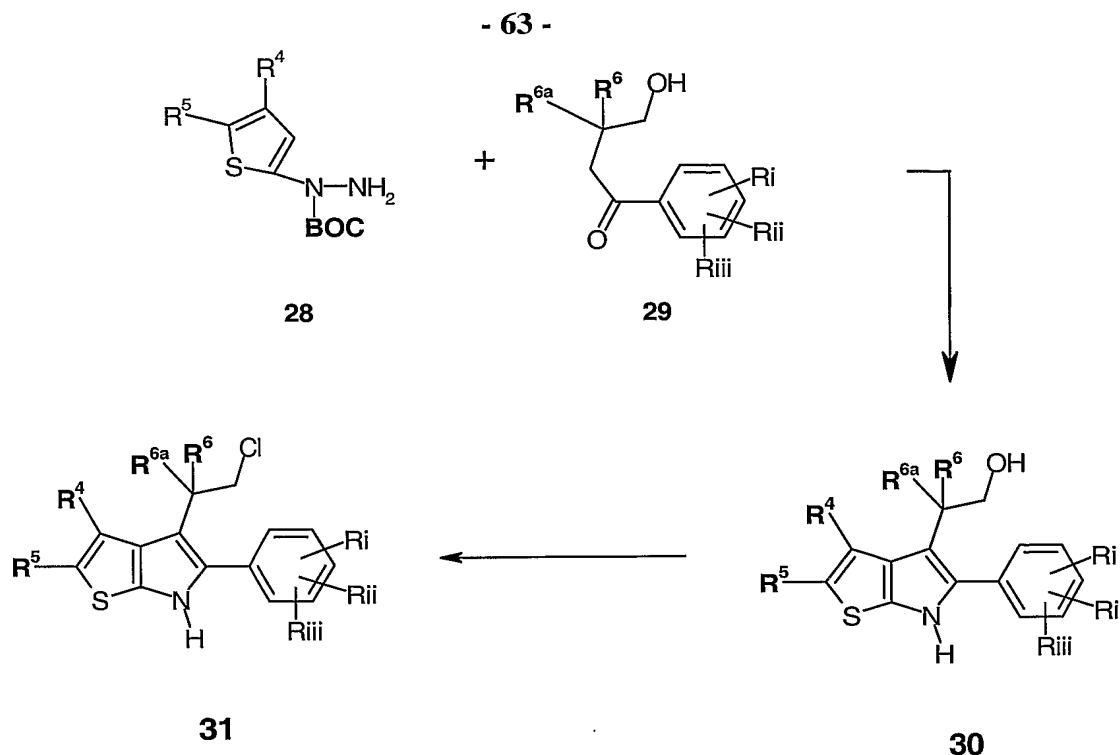
Similarly, reaction with 1,1'-bis(methylthio)-2-nitroethylene in an inert solvent such as methylene chloride, chloroform, benzene, tetrahydrofuran and the like, followed by condensation with an appropriately substituted amine in an inert organic solvent from the list above yields the nitroethyleneimidazo[1,2-a]pyridine **25** (Scheme j, **20**→**24**→**25**).

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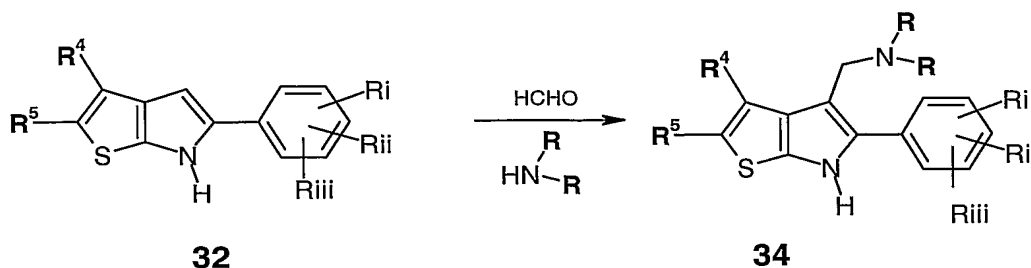
Scheme k.

Again in a similar fashion the suitable thienopyrrole **20**, derived from de-protection, can be converted to a urea by either direct treatment with an iso-cyanate in an inert solvent such as methylene chloride, chloroform or THF and the such like, or by a two step procedure of reaction with triphosgene (**20**→**27**) followed by addition of an amine (**27**→**26**), bearing the required substitution to yield **26**.



Scheme 1.

Chloro thieno-pyrrole intermediates, such as **31**, can be made as shown in Scheme 1. **30** can be synthesized by the classic Fisher thieno-pyrrole synthesis reaction by the condensation of a hydrazine-HCl **28** and a ketone **29**, bearing hydrogen atoms  $\alpha$  to the carbonyl. Treatment of these reactants in a suitable solvent, such as acetic acid, ethanol, *sec*-butanol, toluene, in the presence of an acid, such as sulphuric, hydrochloric, polyphosphoric and/or a Lewis acid, for example, boron trifluoride, zinc chloride, magnesium bromide, at elevated temperatures (for example 100 °C), gives the desired product. The chloro intermediate **31** can then be synthesized from **30** using, for example, either (i) sulphonyl chloride in methylene chloride at a temperature of about 0°C, or (ii) CCl<sub>4</sub> followed by triphenylphosphine in a solvent such as acetonitrile at a temperature of about 0°C. Thienopyrroles of the invention can then be prepared by displacement of chlorine atom using an appropriate side chain intermediate such as a substituted heterocyclic ring.



Scheme m.



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Thienopyrroles of Formula (I) wherein A is a direct bond and R<sup>6</sup> and R<sup>6a</sup> are both hydrogen can be prepared as shown in Scheme m. A thieno-pyrrole 32 can be reacted with formaldehyde and an amine, in a suitable solvent such as acetic acid/dioxan at a temperature of about 0°C to 25°C for between about 1 to 8 hours, form the thieno-pyrrole 34.

5

**EXAMPLES**

The invention will now be illustrated with the following non-limiting examples in which, unless otherwise stated:

(i) evaporations were carried out by rotary evaporation *in vacuo* and work-up  
10 procedures were carried out after removal of residual solids such as drying agents by filtration;

(ii) operations were carried out at room temperature, that is in the range 18-25°C and under an atmosphere of an inert gas such as argon or nitrogen;

(iii) yields are given for illustration only and are not necessarily the maximum  
15 attainable;

(iv) the structures of the end-products of the Formula (I) were confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; proton magnetic resonance chemical shift values were measured on the delta scale and peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin,  
20 quintet;

(v) intermediates were not generally fully characterised and purity was assessed by thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), infra-red (IR) or NMR analysis;

(vi) chromatography was performed on silica (Merck Keiselgel: Art.9385);

25 (vii) isolate<sup>TM</sup> refers to silica (SiO<sub>2</sub>) based columns with irregular particles with an average size of 50µm with nominal 60 Å porosity [Source: Jones Chromatography, Ltd., Glamorgan, Wales, United Kingdom].

**Abbreviations**

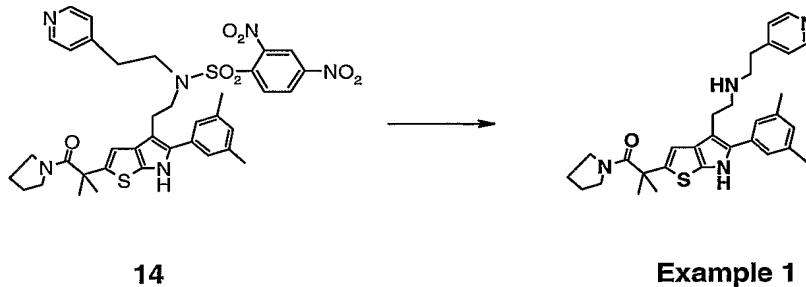
30 DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DEAD	diethylazodicarboxylate
DIPEA	di-isopropylethylamine

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DMA	dimethylacetamide
DMSO	dimethyl sulphoxide
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
5 EDCI	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HOBt	1-hydroxybenzotriazole
THF	tetrahydrofuran

10 **Example 1**

**2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-4-N-(2-pyridin-4-ylethyl)aminoethyl-5-(3,5-dimethylphenyl)--6H-thieno[2,3-b]pyrrole**



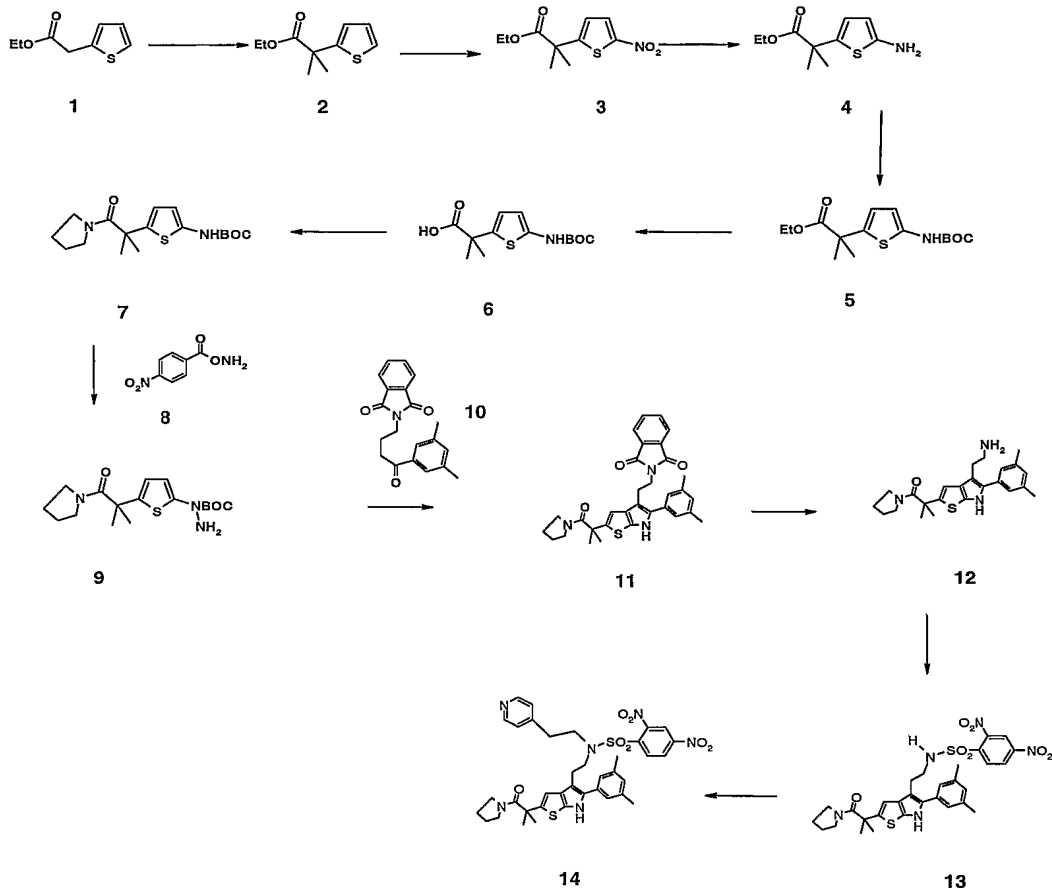
- 15 A solution of **14** (0.486 g; 0.649 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (6 ml) was treated with n-propylamine (0.5 ml). The mixture was stirred at ambient temperature for 1 hour. After evaporation to dryness, the residue was taken up in AcOEt and treated at 0°C with an HCl / ether mixture to give a precipitate which was washed with AcOEt and ether.

Yield: 81 %

- 20 MS-ESI: 515 [M+H]<sup>+</sup> <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 1.55 (s, 6H); 1.64 (m, 4H); 2.33 (s, 6H); 3-3.5 (m, 12H); 9.89 (s, 1H); 6.95 (s, 1H); 7.08 (s, 2H); 7.6-7.9 (br m, 1H); 8.04 (d, 2H); 8.93 (d, 2H).

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The starting material was prepared as follows:



To a suspension of NaH (54 g; 1.35 mol), and 18-crown-6 in THF (2 l) stirred at ambient temperature under argon atmosphere, **1** (100 g; 0.588 mol) was added over a period of 30 minutes. After stirring overnight, the mixture was cooled at 0°C and methyl iodide was added dropwise. The mixture was stirred at 18°C for 3 hours, poured into a saturated solution of NH<sub>4</sub>Cl and extracted with AcOEt. The organic phase was evaporated and purified by flash chromatography eluting with petroleum ether / ethyl acetate 95/5 to give **2** as an oil.

Yield: 90 %

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.20 (t, 3H); 1.63 (s, 6H) ; 4.10 (q, 2H) ; 6.92 (m, 2H) ; 7.17 (m, 1H).

Nitronium tetrafluoroborate (77.9 g; 0.586 mol) was added at -55°C to a solution of **2** (105.6 g; 0.583 mol) in DME (1.5 l). The mixture was allowed to warm up at

-10°C over 4 hours. After extraction with ethyl acetate, the organic phase was purified by flash chromatography, eluting with petroleum ether / AcOEt 95/5 to give **3**.

Yield: 86 %

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<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.23 (t, 3H); 1.65 (s, 6H); 4.14 (q, 2H); 6.90 (d, 1H); 7.75 (d, 1H).

A suspension of **3** (101.7 g; 0.41 mol) and 10 % Pd/C (15 g) in a mixture of ethanol (700 ml) and ethyl acetate (300 ml) was hydrogenated under hydrogen atmosphere

- 5 (5 bars) for 5 hours. After filtration of the catalyst on celite, the residue was evaporated and redissolved in THF (900 ml); di-tert-butyl dicarbonate (100 g; 0.46 mol) was added and the mixture was refluxed for 16 hours. After evaporation of the solvents, the resulting solid was taken up in petroleum ether and filtered to give **5**.

Yield: 68 %

- 10 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.20 (t, 3H); 1.48 (s, 9H); 1.58 (s, 6H); 4.10 (q, 2H); 6.30 (m, 1H); 6.60 (m, 1H).

A solution of **5** (50 g; 0.16 mol) and 2N NaOH (160 ml) in ethanol (300 ml) was refluxed for 1 h 30. After evaporation to dryness, the residue was partitioned between water and ether. The  
15 aqueous layer was acidified with saturated citric acid and extraction with ethyl acetate to give after evaporation a solid, which was triturated in pentane and filtered to give **6** as a solid.

Yield: 100%

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 1.48 (m, 15H); 6.30 (d, 1H); 6.59 (d, 1H).

- 20 A solution of **6** (20.1 g; 0.07 mol), EDCI (20.1 g; 0.105 mol) and DMAP (2.56 g; 0.021 mol) in dichloromethane (200 ml) was stirred under argon atmosphere for 10 minutes. Pyrrolidine (11.69 ml; 0.14 mol) was then added and the mixture was stirred overnight at ambient temperature. After evaporation to dryness, the residue was purified by flash chromatography eluting with AcOEt / petroleum ether 40/60 to give after trituration in  
25 ether / pentane **7** as a solid.

Yield 73%

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.51 and 1.57 (s, 15 H); 1.7 (m, 4H); 3.03 (br, 2H); 3.50 (br, 2H); 6.35 (d, 1H); 6.48 (d, 1H); 7.26 (br, 1H).

- 30 **7** (17 g; 0.05 mol) was added under argon atmosphere to a suspension of NaH 60 % (2.42 g; 0.06 mol) in dioxan (240 ml). The mixture was stirred at 100°C for 3 hours. After cooling to 10°C, **8** (10.1 g; 0.055 mol) was added. The reaction mixture was stirred at ambient temperature overnight. After filtration of the insoluble, the filtrate was evaporated and

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purified by flash chromatography, eluting with AcOEt / petroleum ether 45/55 to give **9** as a white solid.

Yield: 90 %

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.55 and 1.57 (s, 15 H); 1.71 (s, 4H); 3.04 (s, 2H); 3.50 (s, 2H); 6.53 (d, 5 2H); 6.70 (s, 2H).

A solution of **9** hydrochloride salt (4 g; 0.0102 mol) and **10** (6.6 g; 0.0205 mol) in AcOH (20 ml) was heated at 120°C under argon atmosphere for 3 hours. The reaction mixture was diluted with saturated NH<sub>4</sub>Cl and extracted with AcOEt. After evaporation, the crude was 10 purified by flash chromatography eluting with AcOEt / petroleum ether 50/50 to give **11** as a foam.

Yield: 53 %

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.53 and 1.58 (s, 6H); 1.69 (s, 4H); 2.29 (s, 6H); 3.12 (m, 4H); 3.52 (s, 2H); 3.91 (m, 2H); 6.80 (m, 2H); 7.02 (s, 2H); 7.6-7.8 (m, 4H); 8.10 (s, 1H).

15 MS-ESI : 540 [M+H]<sup>+</sup>

A solution of **11** (0.534 g; 0.99 mmol) and hydrazine (1 ml) in a mixture of EtOH (2 ml) and CH<sub>2</sub>Cl<sub>2</sub> (2 ml) was stirred under argon atmosphere at ambient temperature overnight. After evaporation, the crude was extracted in a mixture of CH<sub>2</sub>Cl<sub>2</sub> and saturated 20 NaHCO<sub>3</sub>. The organic layer was evaporated to give **12** as a foam.

Yield: 90 %

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.52 and 1.62 (s, 6H); 1.69 (s, 4H); 2.33 (s, 6H); 2.80-3.2 (m, 6H); 3.52 (m, 2H); 6.74 (s, 1H); 6.93 (s, 1H); 7.05 (s, 2H); 8.15 (s, 1H).

MS-ESI: 410 [M+H]<sup>+</sup>

25

2,4 dinitrobenzylsulfonyl chloride (0.238 g; 0.892 mmol) was added at 0°C, under argon atmosphere to a solution of **12** (0.365 g; 0.892 mmol) and collidine (0.118 ml; 0.892 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 ml). The mixture was stirred at 20°C for 1 hour. After evaporation, the crude was purified by flash chromatography eluting with CH<sub>2</sub>Cl<sub>2</sub> / EtOH 96/4 to give **13**.

30 Yield: 90 %

MS-ESI: 640 [M+H]<sup>+</sup>

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DEAD (0.295 ml; 1.5 mmol) was added at 0°C under argon atmosphere to a solution of **13** (0.48 g; 0.75 mmol), PPh<sub>3</sub> (0.393 g; 1.5 mmol) and 2-hydroxyethyl-4-pyridine (0.185 g; 1.5 mmol) in THF (12 ml). The mixture was stirred at ambient temperature for 2 hours and purified by flash chromatography eluting with AcOEt / petroleum ether 80/20 to give **14**.

5 Yield: 86 %

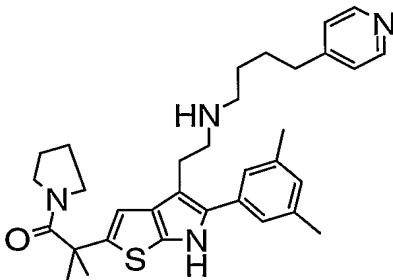
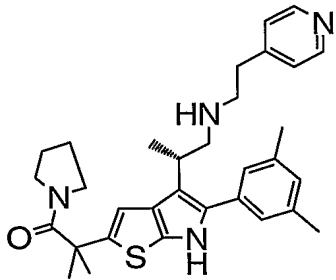
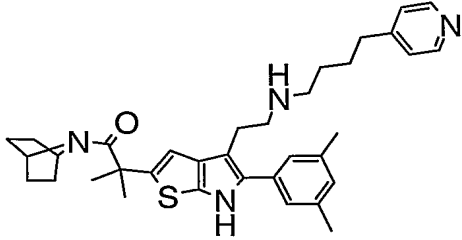
<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.55 (s, 6H) ; 1.55-1.8 (m, 4H) ; 2.3 (s, 6H) ; 2.75 (t, 2H) ; 3-3.2 (m, 4H) ; 3.4-3.7 (m, 6H) ; 6.71 (s, 1H) ; 6.88 (d, 2H) ; 6.93 (s, 1H) ; 6.94 (s, 2H) ; 7.86 (d, 1H) ; 8.20-8.25 (m, 2H) ; 8.31 (s, 1H) ; 8.43 (d, 2H).

10 **Examples 1.1 – 1.12**

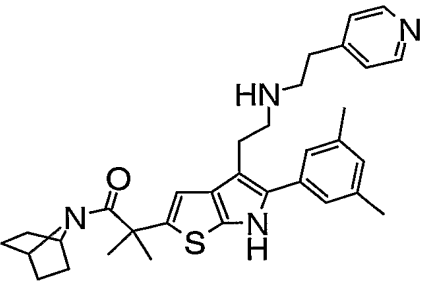
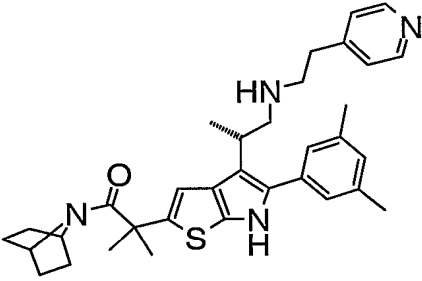
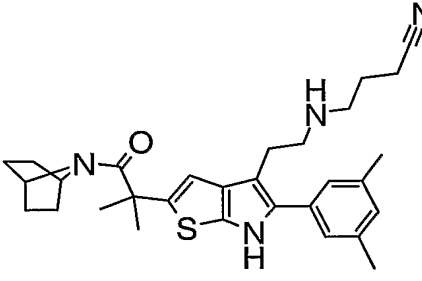
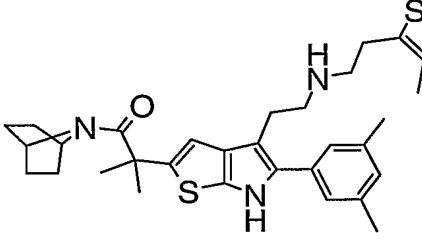
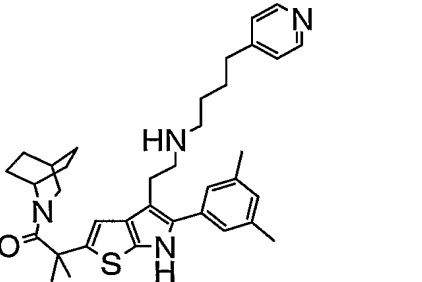
Following a procedure similar to that described in Example 1, the compounds of Table1 were prepared and purified by flash chromatography eluting with a gradient of 0-5% 3.5N NH<sub>3</sub>-MeOH / CH<sub>2</sub>Cl<sub>2</sub>

15

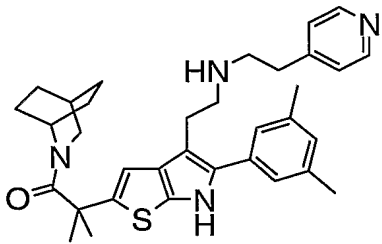
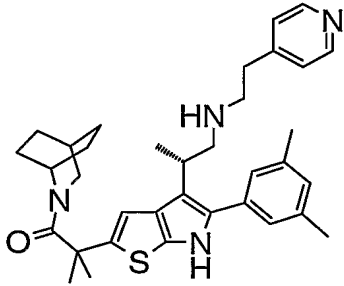
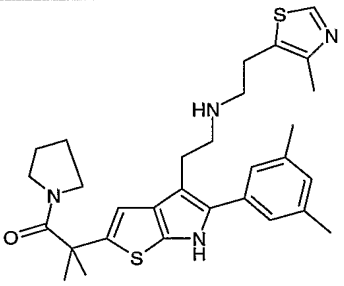
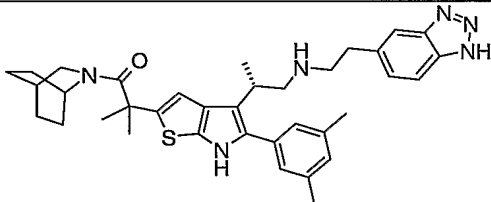
**Table1**

Example		MS-ESI
1.1		543 [M+H] <sup>+</sup>
1.2		529 [M+H] <sup>+</sup>
1.3		569 [M+H] <sup>+</sup>

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Example		MS-ESI
1.4		541 [M+H] <sup>+</sup>
1.5		555 [M+H] <sup>+</sup>
1.6		503 [M+H] <sup>+</sup>
1.7		561 [M+H] <sup>+</sup>
1.8		583 [M+H] <sup>+</sup>

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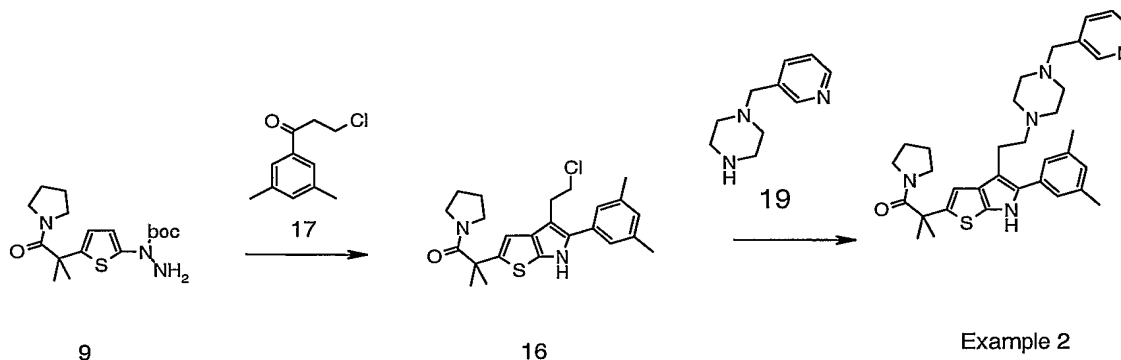
Example		MS-ESI
1.9		555 [M+H] <sup>+</sup>
1.10		569 [M+H] <sup>+</sup>
1.11		534 [M+H] <sup>+</sup>
1.12		609 [M+H] <sup>+</sup>



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**Example 2**

**2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-4-{2-[1-(pyridin-3-ylmethyl)piperazin-4-yl]ethyl}-5-(3,5-dimethylphenyl)--6H-thieno[2,3-*b*]pyrrole**



5 A mixture of **16** (0.362 g; 0.844 mmol), **17** (0.3 g; 1.68 mmol), K<sub>2</sub>CO<sub>3</sub> (0.233 g; 1.68 mmol) in acetonitrile (6 ml) was heated at 85°C under argon atmosphere for 5 hours. The mixture was extracted with AcOEt and the organic layer was evaporated and purified by flash chromatography, eluting with CH<sub>2</sub>Cl<sub>2</sub> 3.5N NH<sub>3</sub> in MeOH 95/5 to give after trituration with ether-pentane **Example 2** as a solid.

10 Yield: 62 %

MS-ESI: 570 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.64 (s, 6H) ; 1.6-1.7 (br m, 4H) ; 2.34 (s, 6H) ; 2.4-2.8 (m, 10H) ; 2.9-3 (m, 2H) ; 3.1-3.2 (m, 2H) ; 3.45-3.65 (m, 4H) ; 6.74 (s, 1H) ; 6.94 (s, 1H) ; 7.05 (s, 2H) ; 7.67 (d, 2H) ; 8.2 (s, 1H) ; 8.5 (d, 2H).

15

The starting material was prepared as follows:

A solution of **9** hydrochloride salt (2 g; 0.005 mol), **15** (2.16 g; 0.01 mol) in sec-butanol (5 ml) was heated at 105°C under argon atmosphere for 2 hours and at 60°C overnight. The solvent was evaporated and the residue purified by flash chromatography eluting with

20 petroleum ether / AcOEt 60/40 to give **16**.

MS-ESI: 429 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (DMSO d<sub>6</sub>) : 1.53 (s, 6H) ; 1.64 (br m, 4H) ; 2-2.15 (m, 1H) ; 2.3 (s, 6H) ; 2.4-2.5 (br m, 1H) ; 3-3.10 (m, 4H) ; 3.35-3.5 (m, 7H) ; 3.8 (br m, 2H) ; 6.83 (s, 1H) ; 6.91 (s, 1H) ; 7.09 (s, 2H).

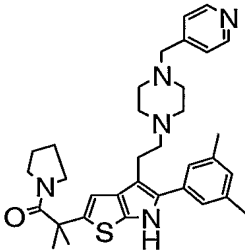
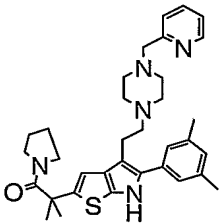
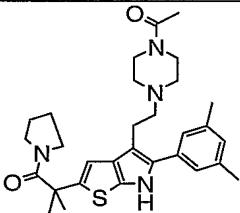
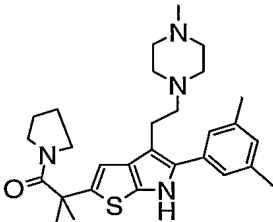
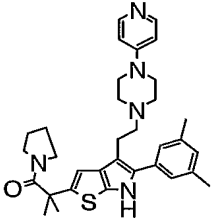
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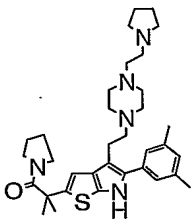
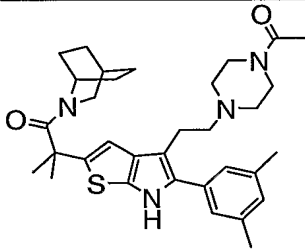
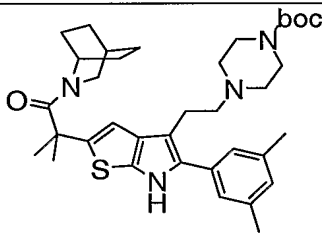
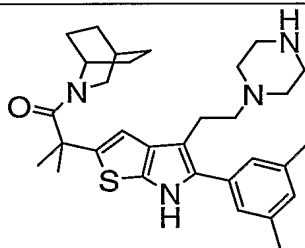
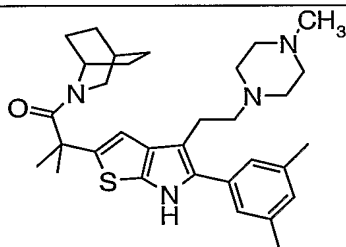
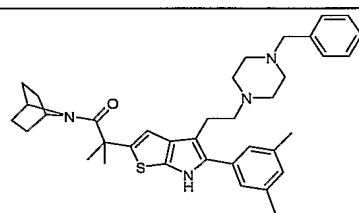
**Examples 2.1 – 2.41**

Following a procedure similar to that described in **Example 2**, the compounds of table 2 were prepared.

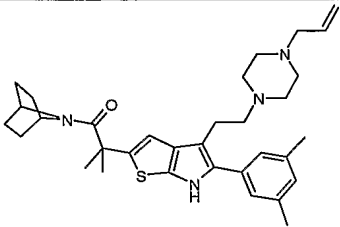
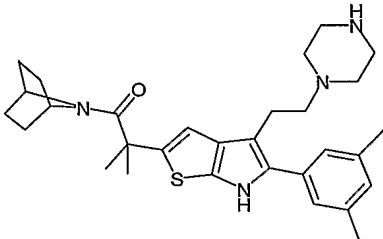
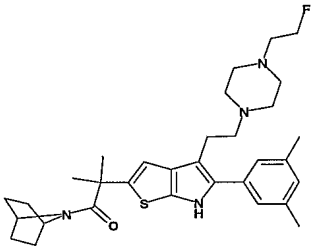
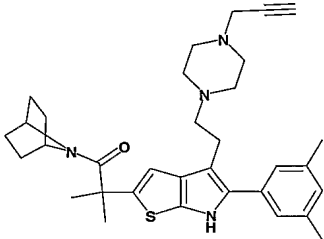
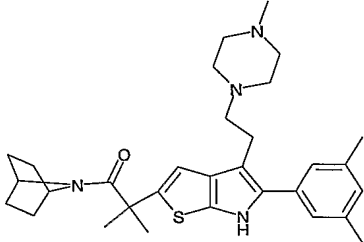
**Table 2**

Example		MS-ESI
2.1		$[M+H]^+$ 570
2.2		570 $[M+H]^+$
2.3		521 $[M+H]^+$
2.4		493 $[M+H]^+$
2.5		556 $[M+H]^+$

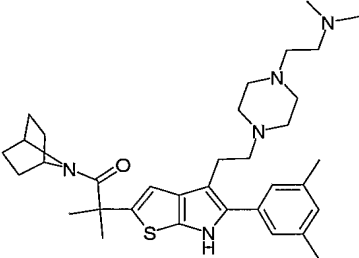
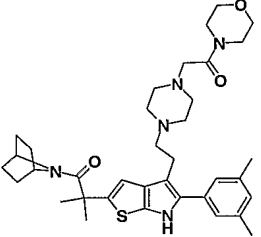
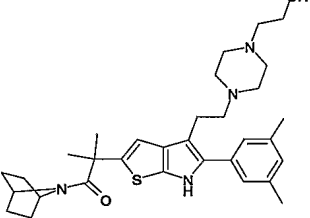
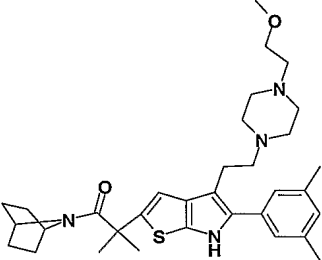
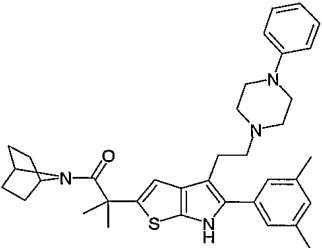
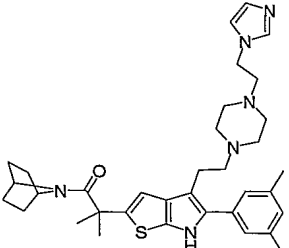
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Example		MS-ESI
2.6		576 [M+H] <sup>+</sup>
2.7		561 [M+H] <sup>+</sup>
2.8		619 [M+H] <sup>+</sup>
2.9		519 [M+H] <sup>+</sup>
2.10		533 [M+H] <sup>+</sup>
2.11		595 [M+H] <sup>+</sup>

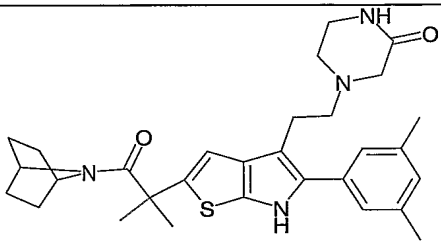
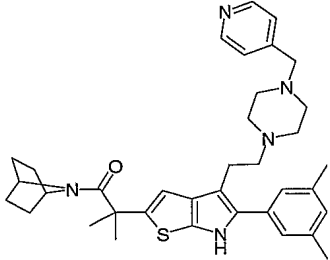
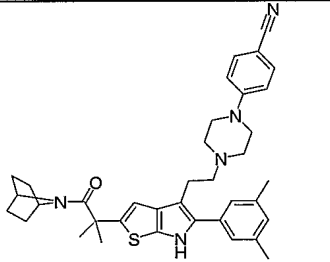
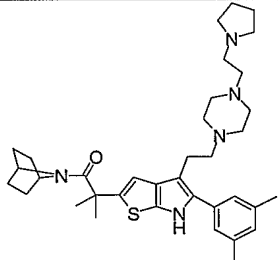
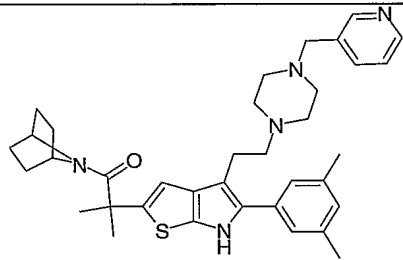
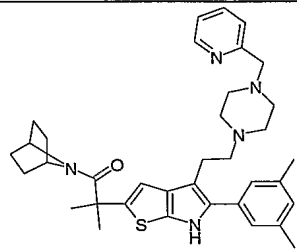
- 75 -

Example		MS-ESI
2.12		545 [M+H] <sup>+</sup>
2.13		505 [M+H] <sup>+</sup>
2.14		551 [M+H] <sup>+</sup>
2.15		543 [M+H] <sup>+</sup>
2.16		519 [M+H] <sup>+</sup>

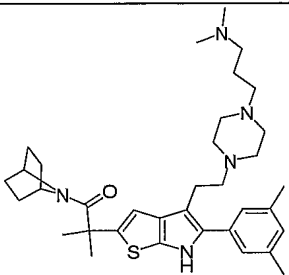
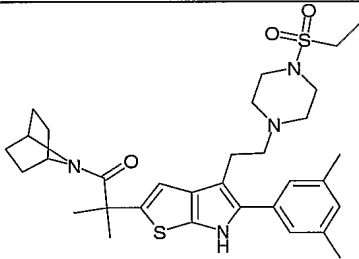
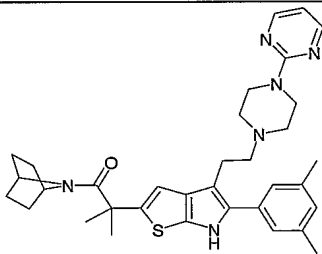
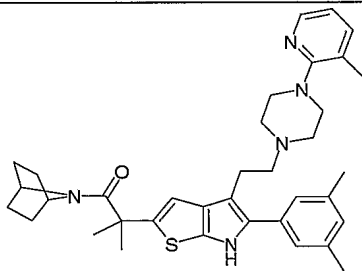
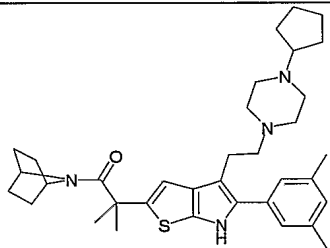
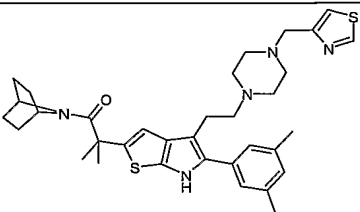
- 76 -

Example		MS-ESI
2.17		576 [M+H] <sup>+</sup>
2.18		632 [M+H] <sup>+</sup>
2.19		549 [M+H] <sup>+</sup>
2.20		563 [M+H] <sup>+</sup>
2.21		582 [M+H] <sup>+</sup>
2.22		599 [M+H] <sup>+</sup>

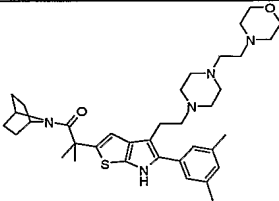
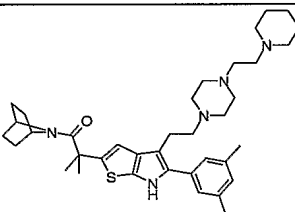
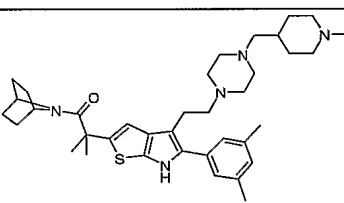
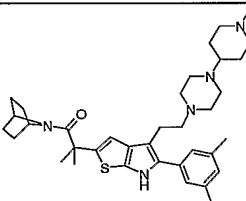
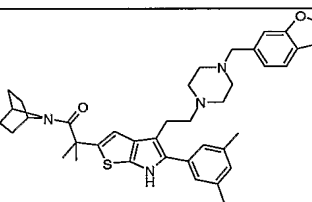
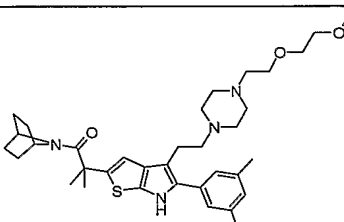
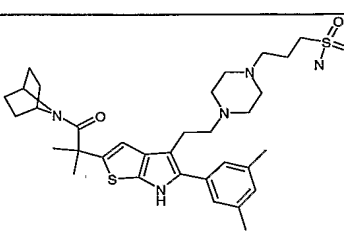
- 77 -

Example		MS-ESI
2.23		519 [M+H] <sup>+</sup>
2.24		596 [M+H] <sup>+</sup>
2.25		606 [M+H] <sup>+</sup>
2.26		602 [M+H] <sup>+</sup>
2.27		596 [M+H] <sup>+</sup>
2.28		596 [M+H] <sup>+</sup>

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Example		MS-ESI
2.29		590 [M+H] <sup>+</sup>
2.30		597 [M+H] <sup>+</sup>
2.31		583 [M+H] <sup>+</sup>
2.32		596 [M+H] <sup>+</sup>
2.33		573 [M+H] <sup>+</sup>
2.34		602 [M+H] <sup>+</sup>

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Example		MS-ESI
2.35		618 [M+H] <sup>+</sup>
2.36		616 [M+H] <sup>+</sup>
2.37		616 [M+H] <sup>+</sup>
2.38		602 [M+H] <sup>+</sup>
2.39		639 [M+H] <sup>+</sup>
2.40		607 [M+H] <sup>+</sup>
2.41		626 [M+H] <sup>+</sup>

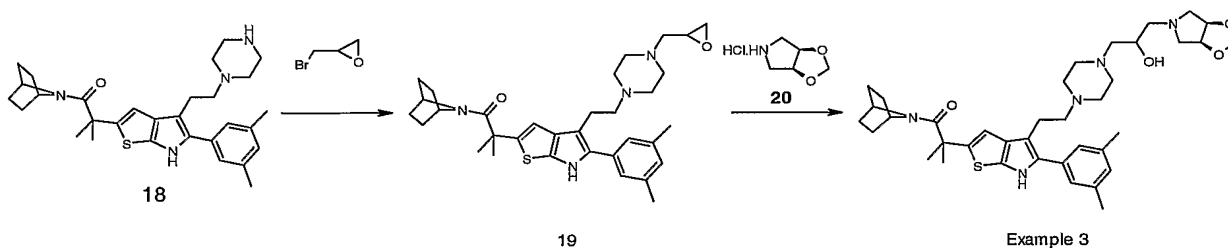


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Example 2.9 was obtained by deprotection of example 2.8 in the presence of TFA in methylene chloride

**Example 3**

- 5 **2-[1,1-dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-{4-(2-hydroxy-3-  
{(3a*R*,6a*S*)-tetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrol-5-yl}-prop-1-yl)piperazin-1-yl}ethyl]  
-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole**



- 10 A mixture of **19** (0.187 g; 0.33 mmol), amino hydrochloride salt **20** (0.152 g; 1.00 mmol) and triethylamine (0.140 ml; 1.00 mmol) in ethanol (2 ml) was heated at reflux for 2 hours. The mixture was concentrated and purified by flash chromatography, eluting with CH<sub>2</sub>Cl<sub>2</sub> 3.5N NH<sub>3</sub> in MeOH 100/0 to 90/10 to give after trituration with ether-pentane Example **3** as a white solid.

- 15 Yield: 40 %

MS-ESI: 676 [M+H]<sup>+</sup>

- <sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.25-1.31 (m, 4H) ; 1.50-1.71 (m, 4H) ; 1.62 (s, 6H) ; 2.24 (d, 1H) ; 2.32 (m, 1H) ; 2.35 (s, 6H) ; 2.38-2.63 (m, 12H) ; 2.68 (m, 2H) ; 2.93 (m, 2H) ; 3.18 (d, 2H) ; 3.84 (m, 1H) ; 4.11 (br s, 1H) ; 4.58 (s, 2H) ; 4.72 (br s, 1H) ; 4.92 (s, 1H) ; 5.09 (s, 1H) ; 6.74 (s, 20 1H) ; 6.94 (s, 1H) ; 7.06 (s, 2H) ; 8.13 (s, 1H).

**19** was prepared as follows:

- To a mixture of **18** (1.75 g ; 3.4 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.55 g ; 4.0 mmol) in dimethylacetamide (15 ml) was added epibromohydrine (0.35 ml ; 4.0 mmol). The mixture was heated at 85°C  
25 under argon atmosphere for 6 hours. After cooling, water was added and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried with MgSO<sub>4</sub>, evaporated and purified by flash chromatography, eluting with CH<sub>2</sub>Cl<sub>2</sub> .MeOH 95/5 to 93/7 to give **19** as a orange foam.

Yield: 78 %

- 30 MS-ESI: 561 [M+H]<sup>+</sup>

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$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.31-2.17 (m, 14H) ; 2.35 (s, 6H) ; 2.17-2.33 (m, 2H) ; 2.49-2.79 (m, 12H) ; 2.94-3.11 (m, 2H) ; 3.11 (m, 1H) ; 4.23 (br m, 1H) ; 4.51 (br m, 1H) ; 6.75 (s, 1H) ; 6.94 (s, 1H) ; 7.07 (s, 2H) ; 8.14 (br m, NH).

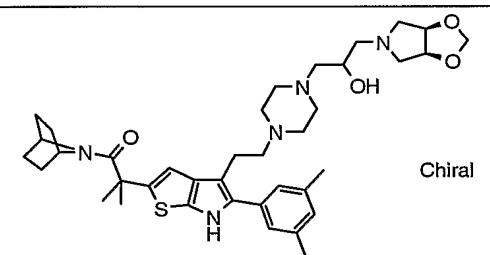
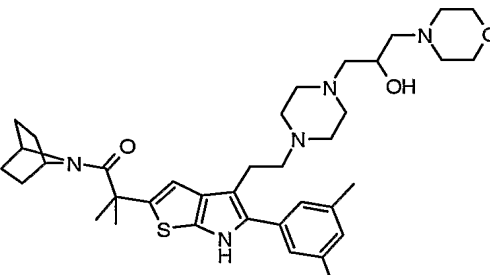
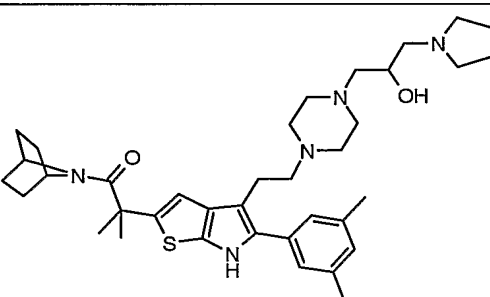
5 The synthesis of **18** is described in example 11.

### Examples 3.1-3.11

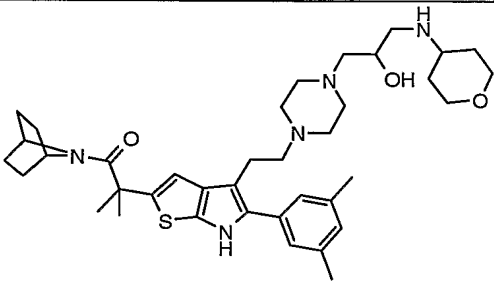
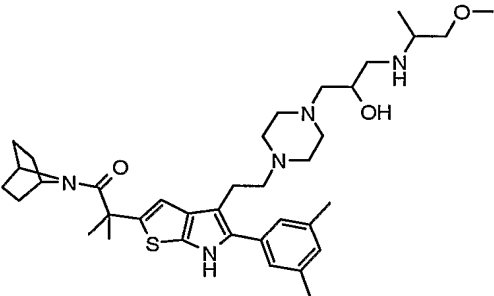
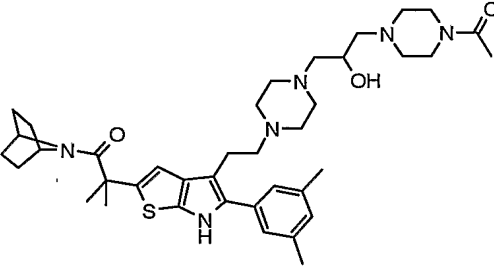
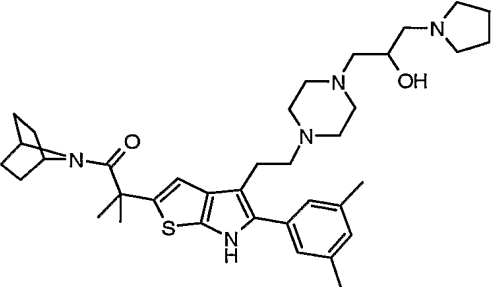
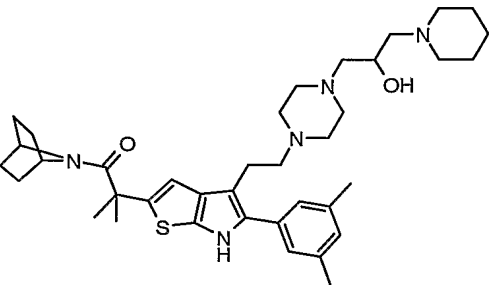
Following a procedure similar to that described in Example 3 , the compounds of table 3 were prepared.

10

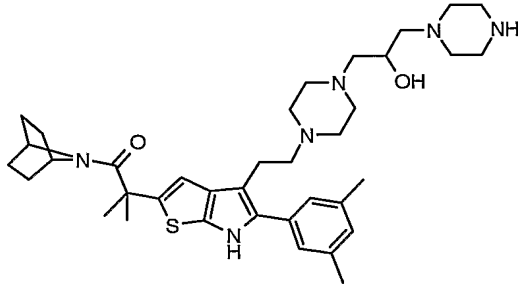
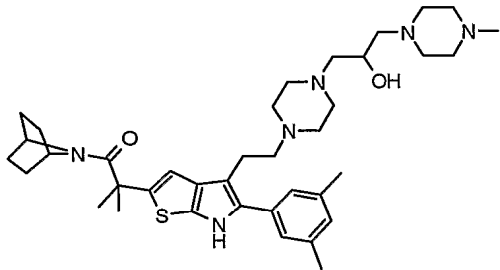
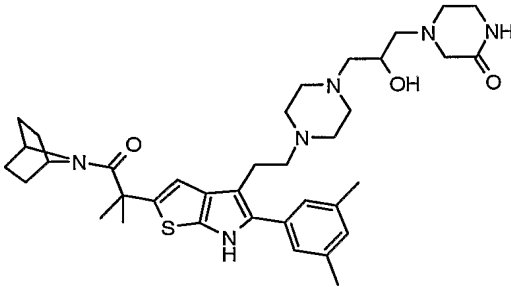
Table 3

Example		MS-ESI
3.1	 <p>Chiral</p>	676 $[\text{M}+\text{H}]^+$
3.2		648 $[\text{M}+\text{H}]^+$
3.3		634 $[\text{M}+\text{H}]^+$

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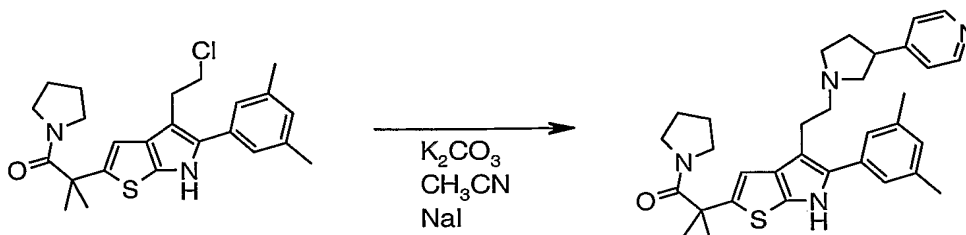
Example		MS-ESI
3.4		662 [M+H] <sup>+</sup>
3.5		650 [M+H] <sup>+</sup>
3.6		689 [M+H] <sup>+</sup>
3.7		632 [M+H] <sup>+</sup>
3.8		646 [M+H] <sup>+</sup>

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Example		MS-ESI
3.9		647 [M+H] <sup>+</sup>
3.10		661 [M+H] <sup>+</sup>
3.11		661 [M+H] <sup>+</sup>

**Example 4**

2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-[2-(3-pyridin-4-ylpyrrolidin-1-yl)ethyl]-6H-thieno[2,3-b]pyrrole



16

Example 4

A mixture of **16** (0.3 g; 0.7 mmol), 4-pyrrolidin-3-yl pyridine (0.31 g, 2.1 mmol), K<sub>2</sub>CO<sub>3</sub> (0.29 g; 2.1 mmol) and NaI (0.314 g; 2.1 mmol) in acetonitrile (10 ml) was heated at 70°C

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under argon atmosphere for 20 hours. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$  and the organic layer was evaporated and purified by flash chromatography eluting with a gradient 5-10 %  $\text{MeOH} / \text{CH}_2\text{Cl}_2$  to give **Example 4** as a solid.

Yield: 40 %

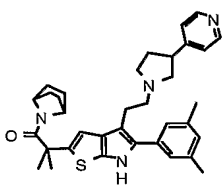
5 MS-ESI: 541  $[\text{M}+\text{H}]^+$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.63 (s, 6H) ; 1.6-1.75 (br m, 4H) ; 1.75-1.95 (m br, 1H) ; 2.31 (s, 6H) ; 2.3-2.35 (br m, 1H) ; 2.58 (m, 1H) ; 2.7-3.2 (m, 9H) ; 3.25-3.35 (m, 1H) ; 3.4-3.6 (m, 2H) ; 6.74 (s, 1H) ; 6.91 (s, 1H) ; 7.05 (s, 2H) ; 7.15 (d, 2H) ; 8.46 (d, 2H) ; 8.53 (s, 1H).

#### 10 Examples 4.1

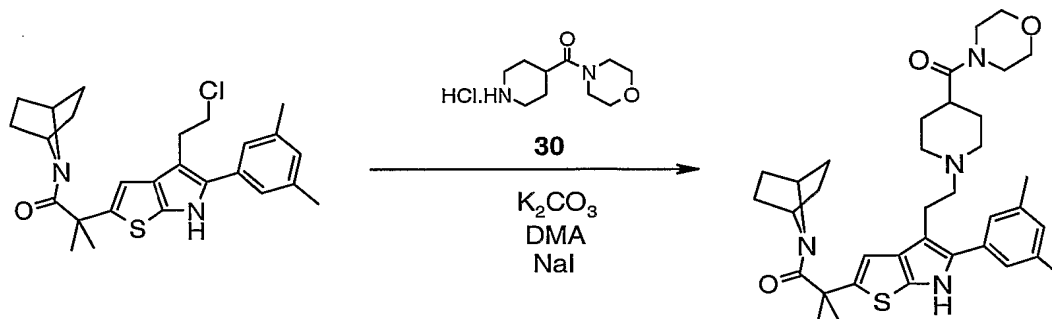
Following a procedure similar to that described in Example 4, example 4.1 were prepared.

**Table 4**

Example		MS-ESI
4.1		567 $[\text{M}+\text{H}]^+$

#### Example 5

15 2-[1,1-dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-(4-{morpholinocarbonyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrole



29

Example 5

A mixture of **29** (0.137 g; 0.3 mmol), **30** (0.150 g, 0.6 mmol),  $\text{K}_2\text{CO}_3$  (0.125 g; 0.9 mmol) and NaI (0.045 g; 0.3 mmol) in dimethylacetamide (3 ml) was heated at  $85^\circ\text{C}$  under argon atmosphere for 6 hours. The crude mixture was purified on preparative LC-MS (column

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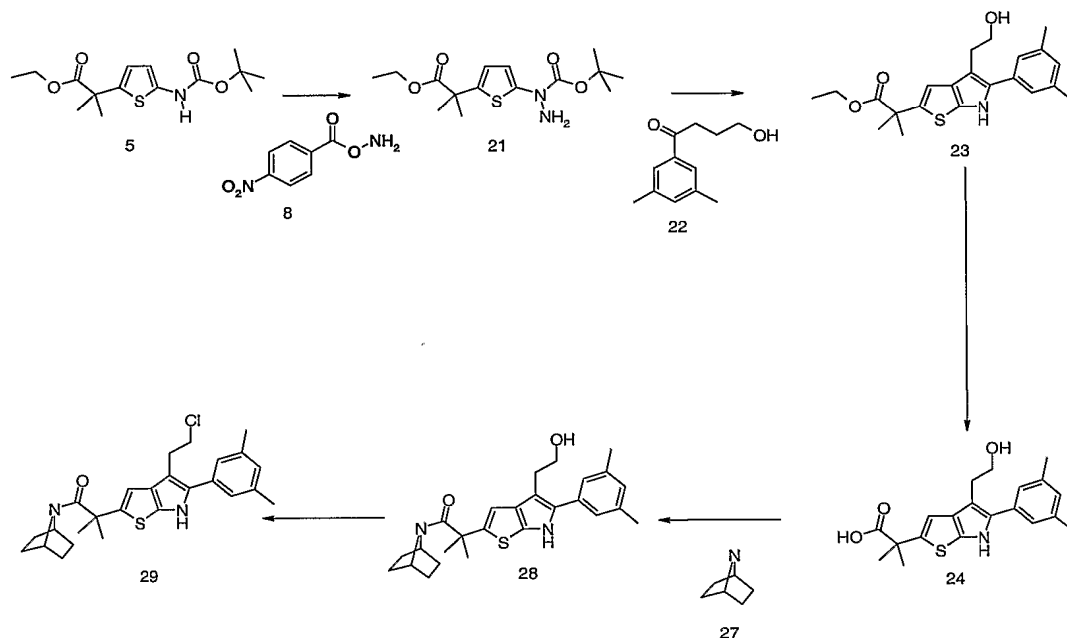
Symetry C<sub>18</sub>, AcOH buffer, H<sub>2</sub>O-CH<sub>3</sub>CN gradient) and the residue was evaporated and crystallized in a pentane- Et<sub>2</sub>O mixture to give Example **5** as a white solid.

Yield: 55 %

MS-ESI: 617 [M+H]<sup>+</sup>

- 5 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.28 (m, 4H) ; 1.62 (s, 6H) ; 1.50-1.75 (m, 6H) ; 1.93 (m, 2H) ; 2.08 (m, 2H) ; 2.35 (s, 6H) ; 2.48 (m, 1H) ; 2.68 (m, 2H) ; 2.97 (br s, 2H) ; 3.09 (m, 2H) ; 3.50 (s, 2H) ; 3.62 (s, 2H) ; 3.68 (s, 4H) ; 4.12 (br s, 1H) ; 4.75 (br s, 1H) ; 6.75 (s, 1H) ; 6.94 (s, 1H) ; 7.06 (s, 2H) ; 8.13 (s, 1H).

10 The intermediate **29** was prepared as follows:



- To a suspension of sodium hydride (44.6 g ; 1.12 mol) in DMF (700 ml) at 10°C, was added a solution of **5** (290 g ; 930 mmol) in DMF (1 l) over a period of 5 minutes. The resulting orange suspension was allowed to warm to room temperature and stirred for 2 hours. The resulting solution was cooled to -5°C in an acetone/ice bath and a solution of **8** (201 g ; 1.02 mol) in DMF (1.4 l) was added over a period of 1 hour. During this period additional DMF (1 l) was added to mobilize the thick precipitate which formed. The resulting suspension was allowed to warm to room temperature and stirred over night after which HPLC showed no remaining starting material. The suspension was poured into water (6 l) and extracted with diethyl ether (3x2 l). The organic extracts were combined and concentrated to approximately 3 l and washed with water (4x1.5 l), a saturated solution of brine (1 l), dried over magnesium sulfate and evaporated to dryness to afford the free base as an off-white solid in quantitative

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yield. To a stirred solution of the free base (150 g ; 457 mmol) in diethyl ether (1.2 l) and heptane (600 ml) at 0°C, was added a 4.0M solution of HCl in 1,4-dioxane (145 ml ; 570 mmol) over a period of 1 hour. The resulting thick, white precipitate was collected by filtration, washed with a mixture of diethyl ether-heptane (1:1, 500 ml) and dried to a constant weight to afford the **21.HCl** (160.3 g) as a white solid.

Yield: 96%

MS-ESI: 328 [M+H]<sup>+</sup>

To a stirred solution of **21** (141 g; 380 mmol) in 2-butanol (1.3 l) was added **22** (104 g; 540 mmol) and zinc chloride (106 g; 770 mmol). The resulting suspension was heated at 100°C for 8 hours after which HPLC showed no remaining starting material. The resulting dark brown solution was evaporated to dryness on a rotary evaporator. The resulting dark brown residue was dissolved in DCM (100 ml), filtered and the filtrate was purified by flash chromatography eluting with DCM, ethyl acetate (9:1) to afford **23** (98 g) as a brown solid.

Yield: 67%

MS-ESI: 386 [M+H]<sup>+</sup>

To a stirred solution of **23** (98 g; 254 mmol) in ethanol (1.8 l) was added 1N NaOH (1.27 l, 1270 mmol). The resulting solution was heated at 60°C for 4 hours after which HPLC showed no remaining starting material. The reaction mixture was cooled to room temperature and the ethanol was removed on a rotary evaporator. The resulting brown solution was cooled to 5°C and concentrated HCl was added dropwise with rapid agitation decreasing the pH to 1. The resulting precipitate was collected by filtration, washed to a neutral pH with water (3x1 l) and dried to a constant weight in a vacuum oven at 50°C to afford **24** as a beige solid (68.3 g).

Yield: 75%

MS-ESI: 358 [M+H]<sup>+</sup>

To a stirred solution of **24** (35.7 g; 100 mmol) and **27** (57 g; 150 mmol) in DCM (1 l) at 0°C, was added DIPEA (70 ml ; 400 mmol) and solid HATU (57 g ; 150 mmol) over a period of 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours after which HPLC showed no remaining starting material. The reaction mixture was washed with a saturated aqueous solution of citric acid (350 ml), a saturated solution of sodium bicarbonate (350 ml) and water (3 x 350 ml). The organic layer was dried over

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anhydrous magnesium sulfate, filtered, and evaporated to dryness on a rotary evaporator. The resulting oily residue was triturated with ethyl acetate (100 ml) and the resulting precipitate collected by filtration and dried to a constant weight in a vacuum oven at 40°C to afford **28** (31.4 g) as a beige solid.

5 Yield: 69%

MS-ESI: 437 [M+H]<sup>+</sup>

To a stirred solution of **28** (29.7 g; 68.1 mmol) in DCM (700 ml) at 0°C was added dropwise neat thionyl chloride (6 ml; 81.7 mmol). The mixture was allowed to warm to room temperature and stirred for a period of 2 h after which HPLC showed no remaining starting material. The reaction mixture was evaporated and purified by flash chromatography, eluting with methylene chloride, AcOEt (9:1) to give **29** as beige foam. The foam was triturated with diethyl ether (100 ml) and the resulting solid collected by filtration, washed with diethyl ether (2 x 50 ml) and dried to a constant weight in a vacuum oven at 40°C to afford **29** as a white solid (26.5 g).

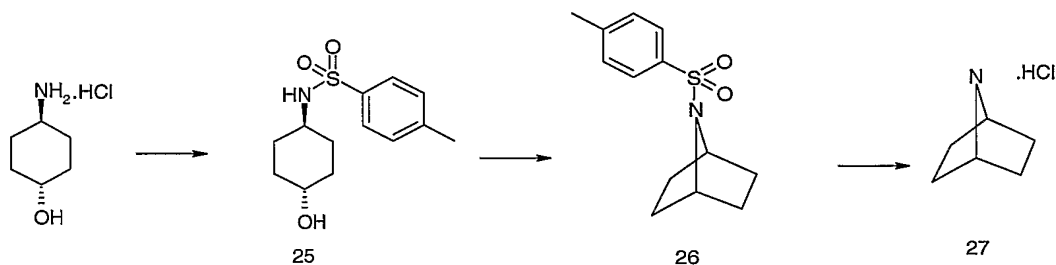
15 Yield : 85%

MS-ESI: 454 [M+H]<sup>+</sup>

<sup>1</sup>H NMR ( DMSO-d<sub>6</sub> ) 1.19–1.41 (m, 4H); 1.45–1.59 (m, 10H); 2.32 (s, 6H); 3.14 (t, 2H); 3.83 (t, 4H); 4.13 (br s, 1H); 4.43 (br s, 1H); 6.89–6.93 (two overlapping s, 2H); 7.08 (s, 2H).

20

The intermediate amine **27** was synthesised as follows:



To a stirred suspension of trans-4-aminocyclohexanol (300 g; 1.98 mol) in isopropanol (3.5 l) at 0°C was added triethylamine (1.1 l; 7.92 mol) followed by solid p-toluenesulfonyl chloride (377 g; 1.98 mmol) over a period of 30 minutes. The reaction mixture was heated at 60°C for 2 hours after which HPLC showed no remaining starting material. The resulting suspension was cooled to room temperature and the precipitate of triethylamine hydrochloride removed by filtration. The filtrate was evaporated to dryness on a rotary evaporator to afford a



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colourless oil which was dissolved in ethyl acetate (3 l), washed with 0.5N HCl (800 ml), water (1.5 l) and dried over MgSO<sub>4</sub>. The solvent was evaporated on a rotary evaporator to afford **25** (456.5 g) as a white crystalline solid.

Yield: 86%

5 MS-ESI: 270 [M+H]<sup>+</sup>

To a stirred solution of **25** (600 g; 2.23 mol) in THF (2 l) at -10°C in an ice/acetone bath, was added triphenylphosphine (700 g; 2.67 mol) followed by di-tert-butylazodicarboxylate (DTBAD) (564 g; 2.45 mol) in THF (1.5 l) over a period of 1.5 hours maintaining the internal  
10 temperature below 10°C. The ice/acetone bath was removed and reaction mixture was allowed to warm to room temperature over a period of 1.5 hours after which HPLC showed no remaining starting material. The reaction mixture was evaporated to dryness and the residue was crystallised from hot MeOH (2.8 l). The resulting crystalline suspension was cooled to 0°C and the crystals collected by filtration, washed with cold MeOH (2 x 200 ml)  
15 and dried to a constant weight in a vacuum oven to afford **26** (378.2 g) as a white crystalline solid routinely contaminated with approximately 10% (w/w) of triphenylphosphine oxide

Yield: 68%

MS-ESI: 252 [M+H]<sup>+</sup>

20 In two separate batches: To a stirred solution of **26** (380 g; 1.51 mol) in THF (3 l) at 0°C was added solid pellets of lithium aluminium hydride (229.4 g; 6.04 mol) over a period of 2 hours under a blanket of nitrogen. The resulting grey suspension was allowed to warm to room temperature and stirred for 4 days after which HPLC showed no remaining starting material. The reaction mixture was diluted with THF (1 l), cooled to 0°C and solid sodium sulfate  
25 decahydrate was added over a period of 2 hours with rapid agitation. When the effervescence had subsided, the resulting suspension was filtered and the filtrate acidified with gaseous HCl affording a thick white precipitate which was collected by filtration, washed with THF (2 x 500 ml) and dried to a constant weight to afford **108** (batch 1: 86.8 g; 43%) (batch 2: 97.3 g; 49%) as a white solid. The filter cakes obtained from the first filtration were suspended in 6N  
30 NaOH (400 ml) and filtered. The filtrate was extracted with diethyl ether (4 l). The organic layer was acidified with gaseous HCl affording a thick white precipitate which was collected by filtration, washed with diethyl ether (2 x 500 ml) and dried to a constant weight in a vacuum oven at 40°C to afford **27.HCl** (105.9 g) as a white solid.

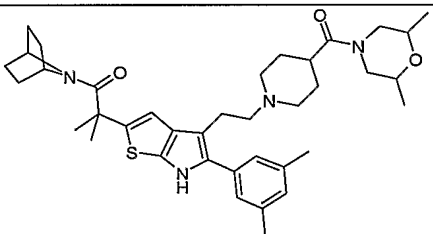
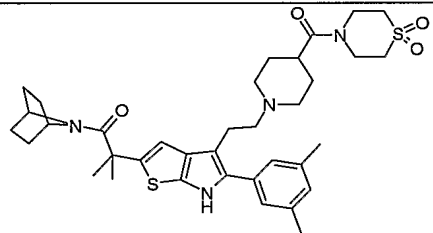
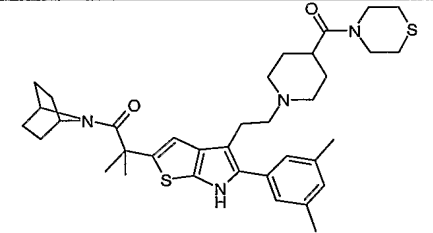
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Yield: 72%

 $^1\text{H}$  NMR ( DMSO- $\text{d}_6$  ) 1.57 (m, 4H); 1.86 (m, 4H); 4.12 (s, 2H); 8.80-9.05 (br s, 1H).**Examples 5.1–5.3**

- 5 Following a procedure similar to that described in **Example 5**, the compounds of table 5 were prepared.

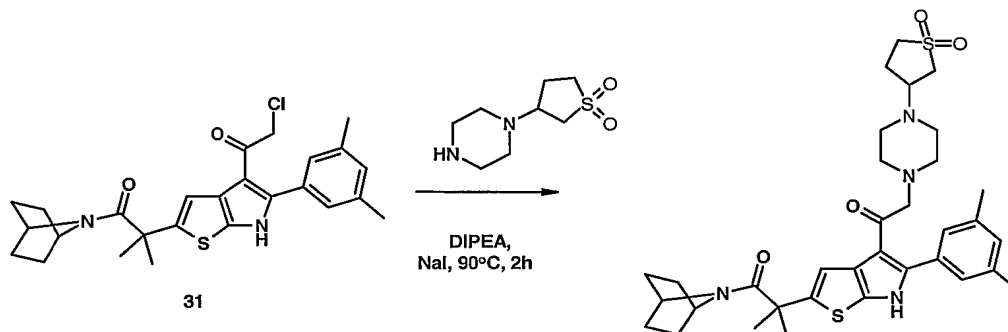
**Table 5**

Example		MS-ESI
5.1		645 $[\text{M}+\text{H}]^+$
5.2		665 $[\text{M}+\text{H}]^+$
5.3		633 $[\text{M}+\text{H}]^+$

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**Example 6**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[1-oxo-2-{4-(1,1-dioxidotetrahydrothien-3-yl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrole**

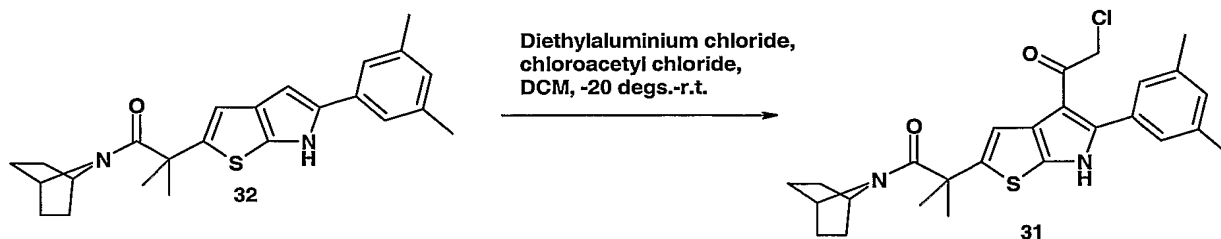


Example 6

5 1-( tetrahydro-1,1-dioxido-3-thienyl)-piperazine (0.044g, 0.22 mmol) was added to a stirred solution of **31** (0.050g, 0.11 mmol), catalytic NaI and diisopropylethyl amine (93μl, 0.55 mmol) in DMF (3ml). After stirring for 2h at 90 °C under nitrogen the reaction mixture was evaporated to dryness under reduced pressure. The residue was partitioned between DCM and  
10 water, the organics were washed with brine, dried and evaporated to dryness. The crude product was purified by chromatography on silica, eluting with 0-10% MeOH/DCM to give example **6** as a yellow foam (0.054g). Yield: 79%

MS-ESI: 637 ( $M^+ + H$ ).

$^1H$  NMR ( $DMSO-d_6$ ) 1.20-1.40 (m, 4H), 1.47-1.80 (m, 10H), 2.00-2.19 (m, 1H), 2.37 (s, 6H),  
15 2.44-2.65 (m, 9H), 2.90-3.10 (m, 2H), 3.15-3.29 (m, 3H), 3.42 (s, 2H), 4.00-5.00 (m, 2H), 7.06 (s, 1H), 7.14 (m, 3H), 8.86 (s, 1H)

**Synthesis of 31**

20 The starting material **31** was prepared as follows:

A 1.0 M solution of diethylaluminium chloride in hexanes(25ml; 25mmol) was added dropwise to a cooled solution of **32** (2.0g; 5.1mmol) in DCM(150ml) stirred under a nitrogen atmosphere at -20 °C The reaction was allowed to warm to 0 °C and kept at this temperature

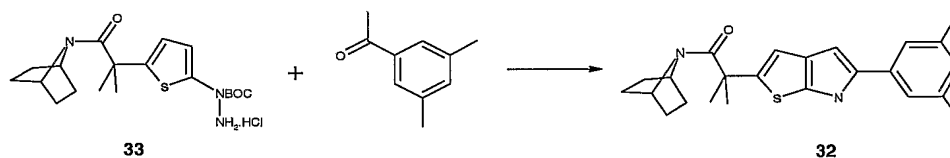
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for 30 mins. It was then cooled back down to  $-20\text{ }^{\circ}\text{C}$  and chloroacetyl chloride (3.4g; 30mmol) was added and the reaction was then warmed to ambient temperature and stirred for a further two hours. It was cooled back to  $-20\text{ }^{\circ}\text{C}$  and water(20ml) was added carefully so that the temperature did not rise above  $-10\text{ }^{\circ}\text{C}$ . It was then warmed to ambient temperature and the organics were separated, dried and evaporated to dryness under reduced pressure. The residue was purified on a silica flash column which was eluted with 10-20% EtOAc/DCM and then EtOAc to give **31** (1.35g) as a pale yellow solid.

MS-ESI: 469.13, 471.12 ( $\text{M}^+ + \text{H}$ ).

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ) 1.54-1.64 (m, 8H), 1.70 (s, 6H), 2.46 (s, 6H), 4.34-4.56 (m, 2H), 4.70 (m, 2H), 7.23 (s, 2H), 7.33 (s, 2H), 12.45 (br s, 1H).

Compound **32** was prepared as follows :



To a stirred solution of **33** (20.75 g, 50 mmol), 3,5-dimethylacetophenone (7.5 g, 50 mmol) and anisole (25 ml) in 2-butanol (25 ml) was slowly added a solution of HCl 4M in dioxane (15 ml). The mixture was warmed up to reflux for 30 minutes. After evaporation of the solvents, the crude product was precipitated in AcOEt, filtered and washed with EtOAc. This crude product was purified by flash chromatography eluting first with a gradient 25/75 to 50/50 AcOEt/ methylene chloride then a gradient 10/40/50 MeOH/ AcOEt/ methylene chloride to give after trituration in methylene chloride **32** as a pale brown solid.

Yield : 19%

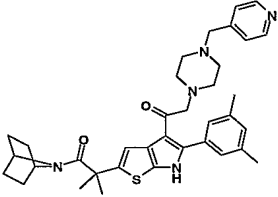
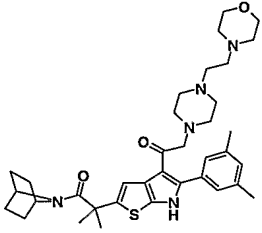
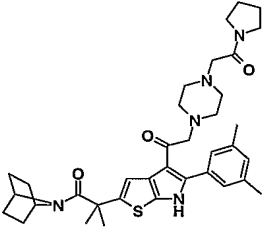
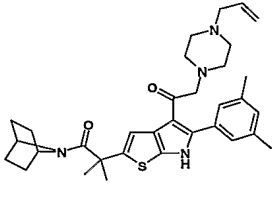
MS-ESI: 393 [ $\text{M} + \text{H}$ ] $^+$

**33** was prepared following a procedure similar to that described for the preparation of intermediate **9** (see Example 1).

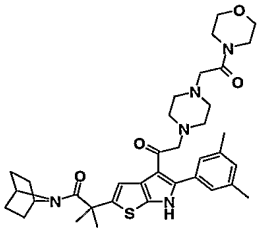
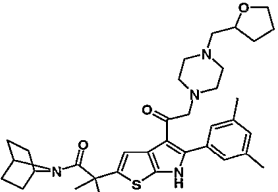
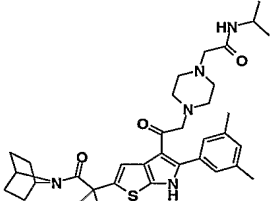
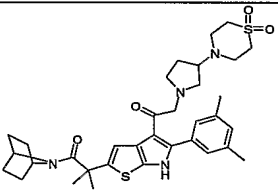
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.32 (m, 4H); 1.52 (s, 9H); 1.56 (s, 6H); 1.50-1.61 (m, 4H); 4.00-5.00 (br m, 1H+1H); 6.60 (s, 1H); 6.94 (s, 1H).

**Examples 6.1-6.31**

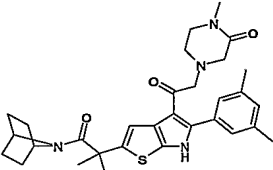
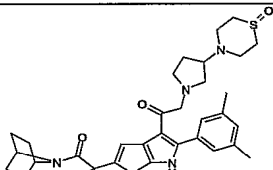
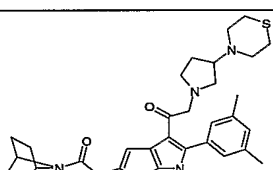
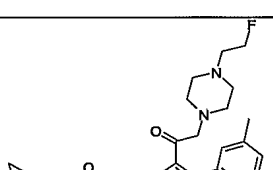
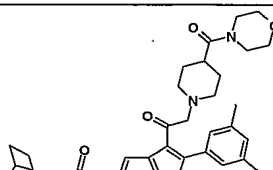
Following a procedure similar to that described in example 6, the compounds of table 6 were prepared.

Example	Structure	<sup>1</sup> H NMR (CDCl <sub>3</sub> )	MS-ESI: (M <sup>+</sup> +H)
6.1		1.19-1.38 (m, 4H), 1.46-1.73 (m, 10H), 2.34 (s, 6H), 2.35-2.58 (m, 8H), 3.42 (d, 4H), 4.00-4.90 (m, 2H), 7.03 (s, 1H), 7.16 (m, 3H), 7.23 (d, 2H), 8.47 (d, 2H), 10.20 (s, 1H)	610
6.2		1.18-1.40 (m, 4H), 1.45-1.80 (m, 10H), 2.34 (s, 6H), 2.35-2.70 (m, 12H), 3.38 (s, 2H), 3.60-3.76 (m, 8H), 3.90-5.00 (m, 2H), 7.06 (s, 1H), 7.15 (m, 3H), 9.48 (s, 1H)	632
6.3		1.15-1.40 (m, 8H), 1.42-1.83 (m, 10H), 2.33 (s, 6H), 2.40-2.65 (m, 6H), 3.07 (s, 2H), 3.38 (s, 2H), 3.38-3.50 (m, 6H), 3.90-5.00 (m, 2H), 7.03 (s, 1H), 7.14 (m, 3H), 9.40 (s, 1H)	630
6.4		1.15-1.36 (m, 4H), 1.45-1.75 (m, 10H), 2.35 (s, 6H), 2.35-2.65 (m, 4H), 2.90-3.00 (m, 4H), 3.37 (s, 2H), 3.80-5.00 (m, 2H), 5.05-5.20 (m, 3H), 5.73-5.90 (m, 2H), 7.04 (s, 1H), 7.14 (s, 3H), 9.70 (s, 1H)	559

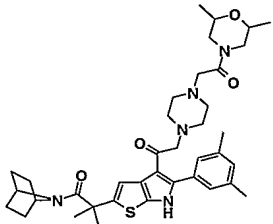
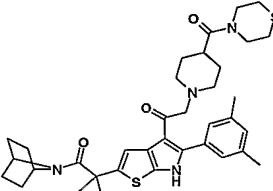
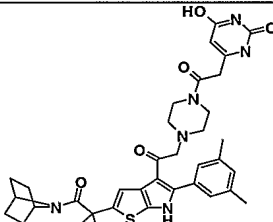
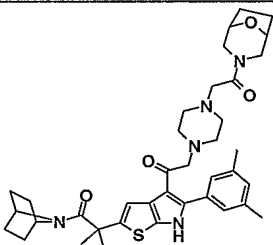
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Example	Structure	<sup>1</sup> H NMR (CDCl <sub>3</sub> )	MS-ESI: (M <sup>+</sup> +H)
6.5		1.20-1.40 (m, 4H), 1.50-1.75 (m, 10H), 2.35 (s, 6H), 2.38-2.57 (m, 8H), 3.10 (s, 2H), 3.39 (s, 2H), 3.50-3.70 (m, 8H), 4.00-5.00 (m, 2H), 7.04 (s, 1H), 7.15 (m, 3H), 9.60 (s, 1H)	646
6.6		1.20-1.37 (m, 4H), 1.38-1.74 (m, 11H), 1.78-1.89 (m, 2H), 1.90-2.00 (m, 1H), 2.32 (s, 6H), 2.35-2.65 (m, 10H), 3.35 (s, 2H), 3.63-3.75 (m, 1H), 3.77-3.90 (m, 1H), 3.91-4.03 (m, 1H), 4.20-5.00 (m, 2H), 7.00 (s, 1H), 7.14 (s, 3H), 10.00 (s, 1H)	603
6.7		1.12 (d, 6H), 1.20-1.40 (m, 4H), 1.45-1.80 (m, 10H), 2.36 (s, 6H), 2.38-2.60 (m, 8H), 2.89 (s, 2H), 3.44 (s, 2H), 3.98-4.14 (m, 1H), 4.15-5.00 (m, 2H), 6.90 (d, 1H), 7.04 (s, 1H), 7.10-7.20 (m, 3H), 9.60 (s, 1H)	618
6.8		1.15-1.40 (m, 4H), 1.45-1.73 (m, 10H), 1.86-1.98 (m, 1H), 2.34 (s, 6H), 2.50-2.75 (m, 5H), 2.80-3.05 (m, 8H), 3.10-3.22 (m, 1H), 3.43 (d, 1H), 3.62 (d, 1H), 4.00-5.00 (m, 2H), 7.04 (s, 1H), 7.10 (s, 1H), 7.18 (s, 2H), 9.62 (s, 1H)	637

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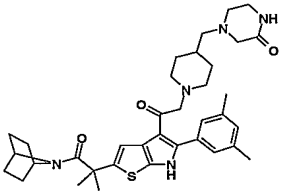
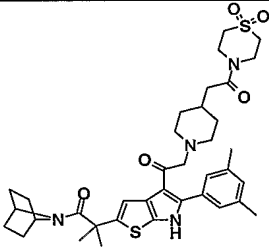
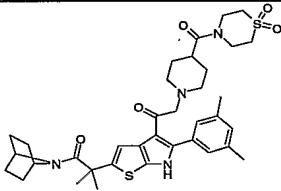
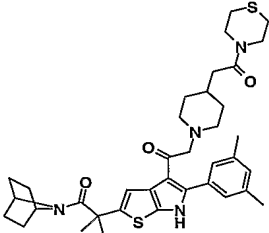
Example	Structure	<sup>1</sup> H NMR (CDCl <sub>3</sub> )	MS-ESI: (M <sup>+</sup> +H)
6.9		1.15-1.40 (m, 4H), 1.45-1.73 (m, 10H), 1.86-1.98 (m, 1H), 2.34 (s, 6H), 2.50-2.75 (m, 5H), 2.80-3.05 (m, 8H), 3.10-3.22 (m, 1H), 3.43 (d, 1H), 3.62 (d, 1H), 4.00-5.00 (m, 2H), 7.04 (s, 1H), 7.10 (s, 1H), 7.18 (s, 2H), 9.62 (s, 1H)	547
6.10		1.16-1.40 (m, 4H), 1.45-1.80 (m, 10H), 1.88-2.00 (m, 1H), 2.35 (s, 6H), 2.46-2.65 (m, 3H), 2.66-2.90 (m, 8H), 2.93-3.13 (m, 3H), 3.47 (d, 1H), 3.61 (d, 1H), 4.00-5.00 (m, 2H), 7.06 (s, 1H), 7.12 (s, 1H), 7.18 (s, 2H), 9.63 (s, 1H)	621
6.11		1.20-1.38 (m, 4H), 1.45-1.75 (m, 10H), 1.84-1.96 (m, 1H), 2.25-2.53 (m, 9H), 2.55-2.80 (m, 10H), 2.83-3.05 (m, 1H), 3.45 (d, 1H), 3.58 (d, 1H), 4.00-5.00 (m, 2H), 7.06 (s, 1H), 7.12 (s, 1H), 7.18 (s, 2H), 9.42 (s, 1H)	605
6.12		1.10-1.30 (m, 4H), 1.40-1.70 (m, 10H), 2.28 (s, 6H), 2.30-2.64 (m, 10H), 3.30 (s, 2H), 4.00-5.00 (m, 4H), 6.97 (s, 1H), 7.08 (m, 3H), 9.51 (s, 1H)	565
6.13		1.18-1.40 (m, 4H), 1.42-1.87 (m, 14H), 2.10-2.22 (t, 2H), 2.24-2.44 (m, 7H), 2.74 (d, 2H), 3.30-3.70 (m, 12H), 4.00-5.00 (m, 2H), 7.00 (s, 1H), 7.16 (s, 3H), 9.90 (s, 1H)	631

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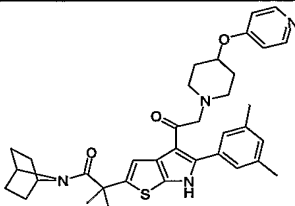
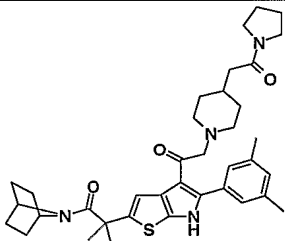
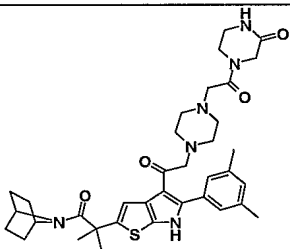
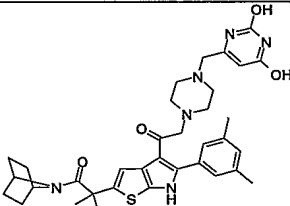
Example	Structure	<sup>1</sup> H NMR (CDCl <sub>3</sub> )	MS-ESI: (M <sup>+</sup> +H)
6.14		1.10-1.40 (m, 10H), 1.45-1.85 (m, 10H), 2.35 (s, 6H), 2.36-2.60 (m, 8H), 2.70 (t, 1H), 3.00-3.70 (m, 7H), 3.93-5.00 (m, 4H), 7.06 (s, 1H), 7.10-7.20 (m, 3H), 8.80 (s, 1H)	674
6.15		1.20-1.40 (m, 4H), 1.45-1.80 (m, 12H), 2.10-2.42 (m, 11H), 2.48-2.67 (m, 4H), 2.70-2.83 (d, 2H), 3.42 (s, 2H), 3.62-3.92 (m, 4H), 4.00-5.00 (m, 2H), 7.04 (s, 1H), 7.15 (s, 3H), 9.48 (s, 1H)	647
6.16		1.20-1.70 (m, 14H), 2.20-3.60 (m, 18H), 3.90-4.70 (m, 2H), 5.30 (s, 1H), 7.03 (s, 1H), 7.09 (s, 1H), 7.20 (s, 2H), 10.70 (s, 1H), 10.90 (s, 1H), 12.15 (s, 1H)	671
6.17		1.18-1.40 (m, 4H), 1.45-1.73 (m, 10H), 1.78-1.98 (m, 4H), 2.32 (s, 6H), 2.35-2.60 (m, 8H), 2.80 (d, 2H), 3.17 (d, 1H), 3.30 (d, 1H), 3.40 (s, 2H), 3.79 (d, 1H), 4.05 (d, 1H), 4.34 (d, 2H), 4.40-5.00 (m, 2H), 7.04 (s, 1H), 7.10-7.20 (m, 3H), 9.75 (s, 1H)	672



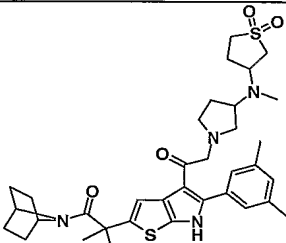
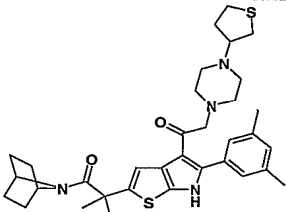
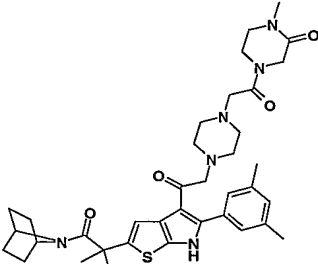
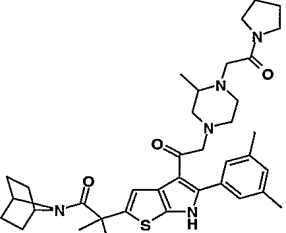
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Example	Structure	<sup>1</sup> H NMR (CDCl <sub>3</sub> )	MS-ESI: (M <sup>+</sup> +H)
6.18		1.15-1.85 (m, 19H), 1.95-2.15 (m, 2H), 2.17-2.26 (d, 2H), 2.36 (s, 6H), 2.60 (m, 2H), 2.75-2.94 (m, 2H), 3.08 (s, 2H), 3.34 (s, 2H), 3.45 (s, 2H), 4.00-5.00 (m, 2H), 5.79 (s, 1H), 7.07 (s, 1H), 7.16 (m, 3H), 8.94 (s, 1H)	630
6.19		1.15-1.40 (m, 8H), 1.45-1.72 (m, 10H), 1.75-1.90 (m, 1H), 2.00-2.18 (m, 2H), 2.27 (d, 2H), 2.34 (s, 6H), 2.80-3.08 (m, 6H), 3.36-3.52 (m, 2H), 3.95 (s, 2H), 4.08 (s, 2H), 4.09-4.80 (m, 2H), 7.05 (s, 1H), 7.15 (m, 3H), 9.60 (s, 1H)	693
6.20		1.20-1.40 (m, 4H), 1.45-1.70 (m, 12H), 1.71-1.80 (m, 2H), 2.25 (t, 2H), 2.35 (s, 6H), 2.37-2.49 (m, 1H), 2.80 (d, 2H), 2.95-3.08 (m, 4H), 3.44 (s, 2H), 3.85-4.13 (m, 4H), 4.14-5.00 (m, 2H), 7.05 (s, 1H), 7.15 (m, 3H), 9.42 (s, 1H)	679
6.21		1.18-1.39 (m, 7H), 1.45-1.86 (m, 12H), 1.93-2.10 (m, 2H), 2.16 (d, 2H), 2.34 (s, 6H), 2.50-2.64 (m, 4H), 2.83 (d, 2H), 3.40 (s, 2H), 3.72 (m, 2H), 3.85 (m, 2H), 4.00-5.00 (m, 2H), 7.04 (s, 1H), 7.14 (m, 3H), 9.74 (s, 1H)	661

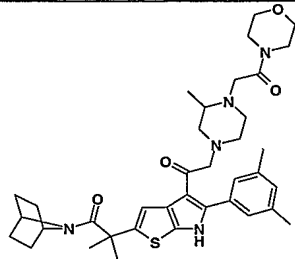
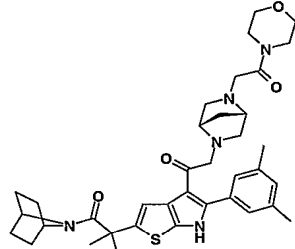
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Example	Structure	<sup>1</sup> H NMR (CDCl <sub>3</sub> )	MS-ESI: (M <sup>+</sup> +H)
6.22		1.18-1.40 (m, 4H), 1.45-1.70 (m, 10H), 1.71-1.86 (m, 2H), 1.90-2.00 (m, 2H), 2.34 (s, 6H), 2.37-2.50 (m, 2H), 2.60-2.73 (m, 2H), 3.47 (s, 2H), 4.00-5.00 (m, 3H), 6.75 (d, 2H), 7.05 (s, 1H), 7.17 (m, 3H), 8.35 (d, 2H), 9.87 (s, 1H)	611
6.23		1.17-1.38 (m, 6H), 1.40-1.73 (m, 12H), 1.74-2.07 (m, 7H), 2.12 (d, 2H), 2.32 (s, 6H), 2.81 (d, 2H), 3.28-3.47 (m, 6H), 4.00-5.00 (m, 2H), 7.02 (s, 1H), 7.14 (m, 3H), 9.92 (s, 1H)	629
6.24		1.17-1.40 (m, 4H), 1.45-1.80 (m, 10H), 2.36 (s, 6H), 2.40-2.65 (s, 7H), 3.18 (d, 2H), 3.30-3.50 (m, 4H), 3.75-3.87 (m, 2H), 4.00-5.00 (m, 4H), 6.20 (d, 1H), 7.06 (s, 1H), 7.15 (m, 3H), 8.94 (d, 1H)	659
6.25		1.18-1.70 (m, 14H), 2.15-2.50 (m, 14H), 3.05-3.50 (m, 4H), 4.00-4.60 (m, 2H), 5.43 (s, 1H), 6.95-7.13 (m, 2H), 7.14-7.30 (s, 2H), 10.60 (s, 1H), 10.90 (s, 1H), 12.15 (s, 1H)	643

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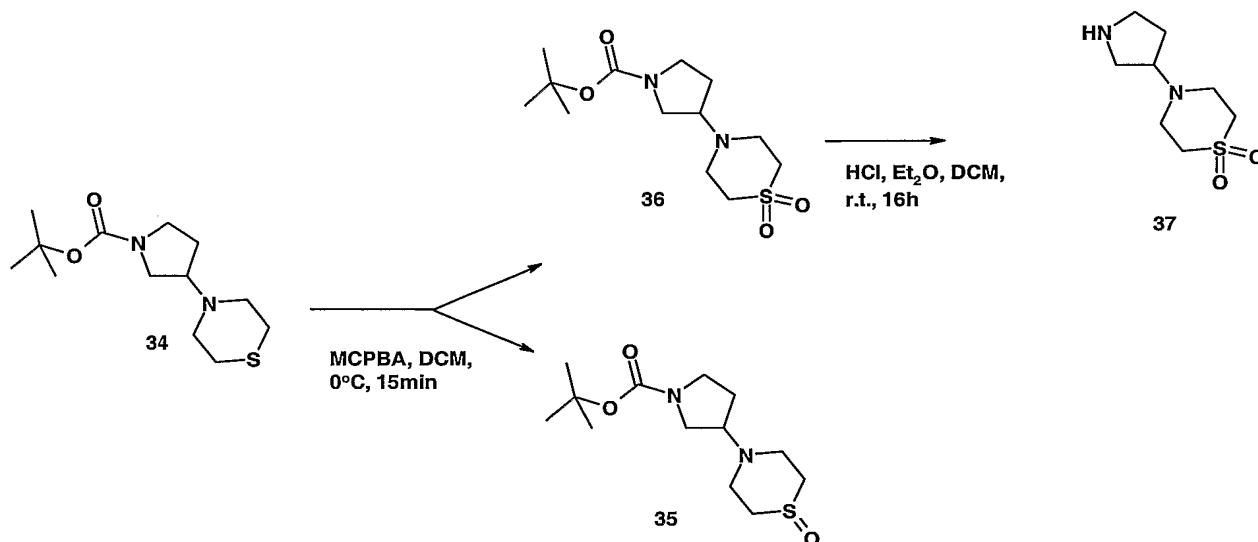
Example	Structure	<sup>1</sup> H NMR (CDCl <sub>3</sub> )	MS-ESI: (M <sup>+</sup> +H)
6.26		1.20-1.40 (m, 4H), 1.44-1.80 (m, 11H), 1.88-2.00 (m, 1H), 2.05-2.19 (m, 1H), 2.23 (d, 3H), 2.24-2.44 (m, 7H), 2.50-3.75 (m, 12H), 4.00-5.00 (m, 2H), 7.07 (s, 1H), 7.13 (s, 1H), 7.18 (s, 2H), 9.22 (s, 1H)	651
6.27		1.18-1.38 (m, 4H), 1.45-1.83 (m, 11H), 2.17-2.27 (m, 1H), 2.35 (s, 6H), 2.38-2.60 (m, 8H), 2.66 (t, 1H), 2.75-2.92 (m, 4H), 3.38 (s, 2H), 4.00-5.00 (m, 2H), 7.04 (s, 1H), 7.15 (m, 3H), 9.76 (s, 1H)	605
6.28		1.20-1.40 (m, 4H), 1.50-1.80 (m, 10H), 2.35 (s, 6H), 2.38-2.60 (m, 8H), 3.00 (s, 3H), 3.10-3.20 (m, 2H), 3.29-3.47 (m, 4H), 3.77-3.90 (m, 2H), 4.13-4.22 (m, 1H), 4.30-5.00 (m, 2H), 7.06 (s, 1H), 7.10-7.20 (m, 3H), 9.10-9.23 (m, 1H)	673
6.29		0.95 (d, 3H), 1.20-1.38 (m, 4H), 1.45-1.70 (m, 10H), 1.75-2.05 (m, 8H), 2.10-2.85 (m, 10H), 3.30-3.70 (m, 7H), 4.00-5.00 (m, 2H), 7.02 (s, 1H), 7.15 (m, 3H), 9.57 (s, 1H)	644

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Example	Structure	$^1\text{H}$ NMR ( $\text{CDCl}_3$ )	MS-ESI: ( $\text{M}^+ + \text{H}$ )
6.30		0.95 (d, 3H), 1.20-1.36 (m, 4H), 1.45-1.70 (m, 10H), 1.90-2.45 (m, 9H), 2.55-2.89 (m, 4H), 3.30-3.88 (m, 12H), 4.00-5.00 (m, 2H), 7.02 (s, 1H), 7.15 (m, 3H), 9.68 (s, 1H)	660
6.31		1.20-1.40 (m, 4H), 1.45-1.85 (m, 10H), 2.35 (s, 6H), 2.65-2.95 (m, 4H), 3.25-3.77 (m, 16H), 4.00-5.00 (m, 2H), 7.06 (s, 1H), 7.10-7.20 (m, 3H), 9.28 (s, 1H)	658

Novel intermediates used in the coupling syntheses were prepared as follows:

### 37 for Example 6.8



5

MCPBA (2.44g, 9.88 mmol) was added to a stirred solution of **34** (1.075g, 3.95 mmol) [see intermediate for Example 6.11] in DCM (15 ml) at 0°C under nitrogen. After stirring for 15min at 0°C the reaction was quenched by the addition of aq. saturated sodium metabisulfite  
 10 (20ml). The phases were separated and the organics were washed with sat.sodium bicarbonate solution (20ml), sat.brine (20ml), dried and evaporated to dryness under reduced pressure.

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The residue was purified by chromatography on silica, eluting with 20% DCM/EtOAc followed by 0-5% MeOH/DCM to give **36** as a yellow solid (0.070g) and **35** as a cream coloured solid (0.65g).

**35**

5 MS-ESI: 289 ( $M^+ + H$ ).

$^1H$  NMR ( $CDCl_3$ ) 1.48 (s, 9H), 1.70-1.90 (m, 1H), 2.00-2.18 (m, 1H), 2.69 (d, 1H), 2.73-3.30 (m, 10H), 3.45-3.80 (m, 2H).

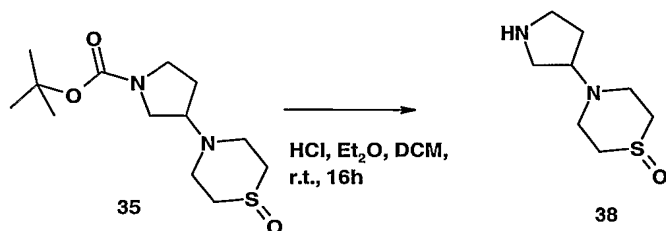
**36**

MS-ESI: 305 ( $M^+ + H$ ).

10  $^1H$  NMR ( $CDCl_3$ ) 1.40-2.15 (m, 11H), 2.93-3.20 (m, 6H), 3.21-3.78 (m, 7H).

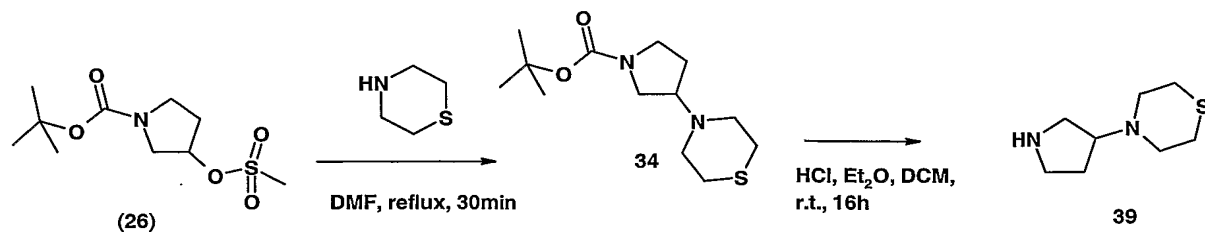
1.0M HCl in  $Et_2O$  (5ml, 5.0 mmol) was added to a solution of **36** (0.122g, 0.40 mmol) in DCM (2ml). After stirring at ambient temperature for 16h the solvent were evaporated away under reduced pressure to give **37** as a yellow solid (0.097g).

15 MS-ESI: 205 ( $M^+ + H$ ).

**38 for Example 6.10**

1.0M HCl in  $Et_2O$  (5ml, 5.0 mmol) was added to a solution of **35** [see intermediate for Example 6.8] (0.1g, 0.35 mmol) in DCM (1ml). After stirring at ambient temperature for 16h the solvents were evaporated under reduced pressure to give **38** as a pale yellow solid (0.078g).

MS-ESI: 189 ( $M^+ + H$ ).

25 **39 for Example 6.11**

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N-(tert(butoxycarbonyl)-3-hydroxypyrrolidine methanesulphonate (2.0g, 7.55 mmol) was added to a solution of thiomorpholine (4ml, 39.8 mmol) in DMF (4 ml). After stirring at reflux (153°C) under nitrogen for 30min the reaction mixture was allowed to cool and evaporated to dryness under reduced pressure. The residue was purified by column chromatography on silica, eluting with 0-10% MeOH/DCM to give **34** as a brown solid (2.1g).

MS-ESI: 274 ( $M^+ + H$ ).

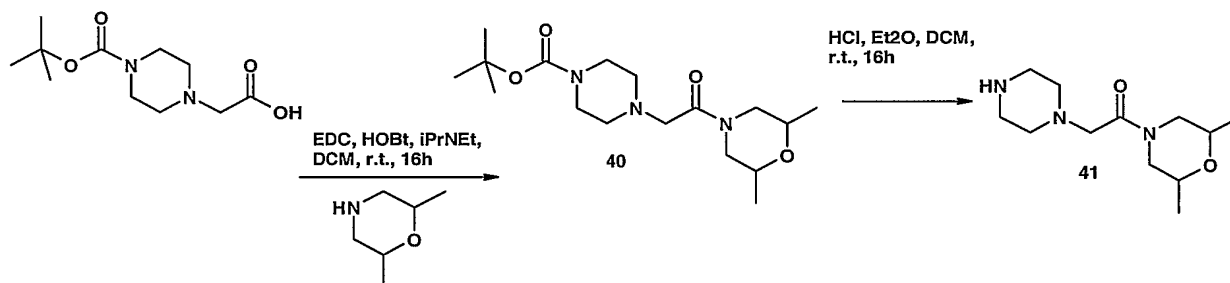
$^1H$  NMR ( $CDCl_3$ ) 1.47 (s, 9H), 1.65-1.85 (m, 1H), 1.86-2.12 (m, 2H), 2.54-3.00 (m, 4H), 3.02-3.16 (m, 1H), 3.19-3.32 (m, 1H), 3.40-3.73 (m, 4H), 3.78-3.88 (m, 2H).

10

1.0M HCl in Et<sub>2</sub>O (8ml, 8.0 mmol) was added to a solution of (27)(0.695g, 2.55 mmol) in DCM (2 ml). After stirring at ambient temperature for 16h the solvents were evaporated away under reduced pressure to give (28) as a pale brown solid (0.53g).

MS-ESI: 173 ( $M^+ + H$ ).

15  $^1H$  NMR ( $CDCl_3$ ) 2.20-4.15 (m, 15H), 9.30-10.20 (m, 1H).

**41 for Example 6.14**

EDC (1.18g, 6.15 mmol) was added to a stirred solution of N-Boc-piperazine acetic acid (1.00g, 4.10 mmol), 2,6-dimethylmorpholine (605μl, 4.92 mmol), 3-hydroxybenzotriazole (0.836g, 6.15 mmol), and diisopropylethylamine (2.14ml, 12.31 mmol) in DCM (30ml) at ambient temperature under nitrogen. After stirring for 16h the reaction was quenched by the addition of water (20ml). The phases were separated and the organics were washed with sat.brine (20ml), dried and evaporated to dryness under reduced pressure. The residue was purified by chromatography on silica, eluting with 0-10% MeOH/DCM to give **40** as a white solid (1.31g).

MS-ESI: 342 ( $M^+ + H$ ).

$^1H$  NMR ( $CDCl_3$ ) 1.20 (d, 6H), 1.46 (s, 9H), 2.34 (dd, 1H), 2.40-2.55 (m, 4H), 2.75 (dd, 1H), 3.10 (d, 1H), 3.27 (d, 1H), 3.35-3.60 (m, 6H), 3.94 (d, 1H), 4.40 (d, 1H).

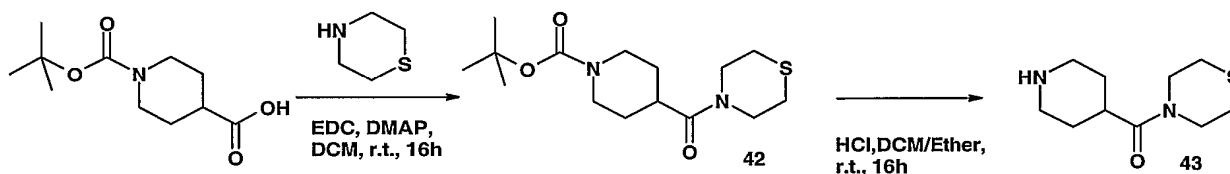
- 102 -

1.0M HCl in Et<sub>2</sub>O (10ml, 10.0 mmol) was added to a solution of **40** (0.58g, 1.70 mmol) in DCM (2 ml). After stirring at ambient temperature for 16h conc. HCl (1ml) was added. After stirring for 2h the solvents were removed under reduced pressure to give **41** as a yellow solid  
5 (0.46g).

MS-ESI: 242 (M<sup>+</sup>+H).

NMR (CDCl<sub>3</sub>,  $\delta$  values) 1.13 (d, 6H), 2.35 (t, 1H), 2.70 (t, 1H), 3.25-3.80 (m, 11H), 4.20 (d, 1H), 4.30-4.48 (m, 1H), 4.50-4.70 (m, 1H), 10.17 (s, 1H).

10 **43** for Example 6.15



A mixture of N-Boc-4-piperidinecarboxylic acid (2.0g, 8.72 mmol), thiomorpholine (1.2g, 11.63mmol), DMAP (4.3g, 35.2 mmol) and EDC (2.2g, 11.48mmol) in dichloromethane (75 ml) was stirred under a nitrogen atmosphere for 16h. The reaction mixture was washed with a  
15 1.0M aq. citric acid solution, sat.sodium bicarbonate solution, the organics separated, dried and evaporated to dryness under reduced pressure. The residue was triturated with Et<sub>2</sub>O to give a white solid, **42** (2.25g).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.44 (s, 9H), 1.55-1.82 (m, 4H), 2.50-2.89 (m, 5H), 2.87 (t, 2H), 3.87-3.97 (m, 4H), 4.04-4.28 (m, 2H).

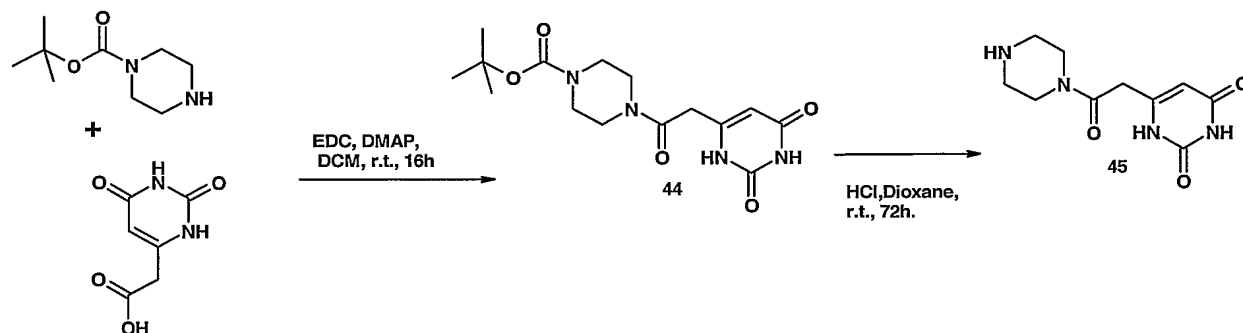
20

A 1.0M solution of HCl in Et<sub>2</sub>O (5 ml, 5mmol) was added to a solution of **42** (0.7g, 2.2mol) in DCM (50ml) and the mixture stirred for 16h under a nitrogen atmosphere. The white precipitate was filtered, washed with Et<sub>2</sub>O and dried to give **43** (0.55g).

MS-ESI: 215 (M<sup>+</sup>+H).

25 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.73 (m, 4H), 2.43-2.69 (m, 4H), 2.80-3.00 (m, 3H), 3.15-3.35 (m, 2H), 3.70 (m, 4H), 8.71 (br s, 1H), 9.09 (br s, 1H).

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45 for Example 6.16

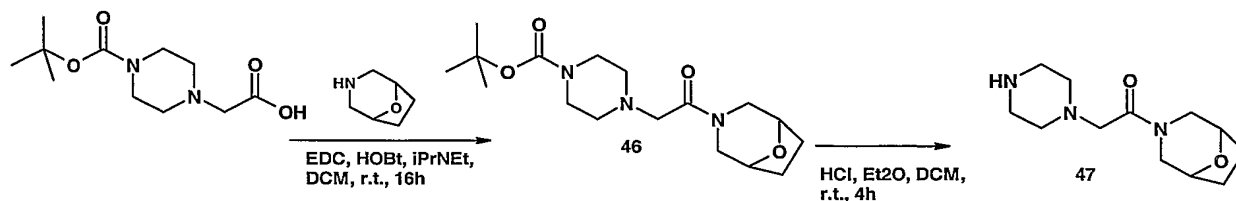
A mixture of N-Boc-piperazine (0.71g, 3.82 mmol), uracil-6-acetic acid (0.5g, 2.94mmol),  
 5 DMAP (1.44g, 11.79 mmol) and EDC (0.736g, 3.84mmol) in dichloromethane (40 ml) was  
 stirred under a nitrogen atmosphere for 16h. The reaction mixture was treated with 1.0M aq.  
 citric acid solution (50ml) to give a white precipitate which was filtered, washed with water,  
 DCM and dried to give **44** (0.375g).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.53 (s, 9H), 3.40-3.60 (m, 8H), 3.62 (s, 2H), 5.44 (s, 1H), 10.81 (br s,  
 10 1H), 11.04 (br s, 1H).

4.0M HCl in dioxane (10 ml, 40mmol) was added to a solution of **44** (0.36g, 1.06 mmol) in  
 dioxane (30 ml) and the mixture stirred for 72h under an atmosphere of nitrogen. The white  
 precipitate was filtered, washed with more dioxane and then with Et<sub>2</sub>O and dried to give **45**  
 15 (0.26g).

MS-ESI: 239 (M<sup>+</sup>+H).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 3.08-3.33 (m, 4H), 3.65 (s, 1H), 3.80 (m, 4H), 5.45 (s, 1H), 9.60 (br s,  
 2H), 10.82 (br s, 1H), 11.05 (br s, 1H).

20 47 for Example 6.17

EDC (1.18g, 6.15 mmol) was added to a stirred solution of N-Boc-piperazine acetic acid  
 (1.00g, 4.10 mmol), 8-oxa-3-aza-bicyclo [3.2.1] octane (0.556g, 4.92 mmol), 3-hydroxy  
 benzotriazole (0.836g, 6.15 mmol), and diisopropylethylamine (2.14ml, 12.31 mmol) in DCM  
 25 (20 ml) at ambient temperature under nitrogen. After stirring for 16h the reaction was



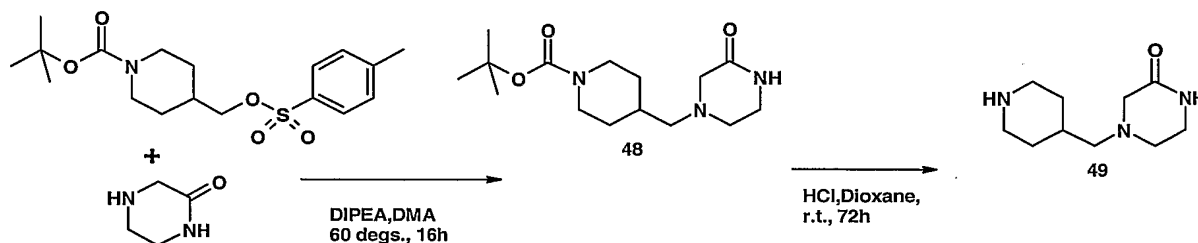
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quenched by the addition of water (20ml). The phases were separated and the organics were washed with sat.brine (20ml), dried and evaporated to dryness under reduced pressure. The residue was purified by chromatography on silica, eluting with 0-10% MeOH/DCM to give **46** as a white solid (0.780g).

5 MS-ESI: 340 ( $M^+ + H$ ).

$^1H$  NMR ( $CDCl_3$ ) 1.45 (s, 9H), 1.80-2.00 (m, 4H), 2.30-2.58 (m, 4H), 2.85-3.04 (m, 2H), 3.25 (d, 1H), 3.30-3.57 (m, 3H), 3.78 (d, 1H), 4.12 (d, 1H), 4.36 (d, 3H).

1.0M HCl in  $Et_2O$  (10ml, 10.0 mmol) and conc HCl (0.5ml) were added to a solution of **46** (0.78g, 2.30 mmol) in DCM (1.5 ml). After stirring at ambient temperature for 4h the solvents were removed under reduced pressure to give **47** as a yellow solid foam (0.633g).

**49 for Example 6.18**

15 A mixture of N-(tert-butoxycarbonyl)-4-(tosyloxymethyl)-piperidine (0.5g, 1.35mmol), piperazin-2-one (0.298g, 2.96mmol), DIPEA (0.525g, 4.06mmol) in DMA (20ml) was stirred at 60°C for 16h under a nitrogen atmosphere. The DMA was evaporated under reduced pressure and the residue portioned between 1.0M aq. citric acid and DCM. The organic layer was separated, dried and evaporated to dryness. It was purified on silica flash column chromatography eluting with EtOAc-20%MeOH/EtOAc to give **48** as a solid foam (0.25g.).

MS-ESI: 298 ( $M^+ + H$ ).

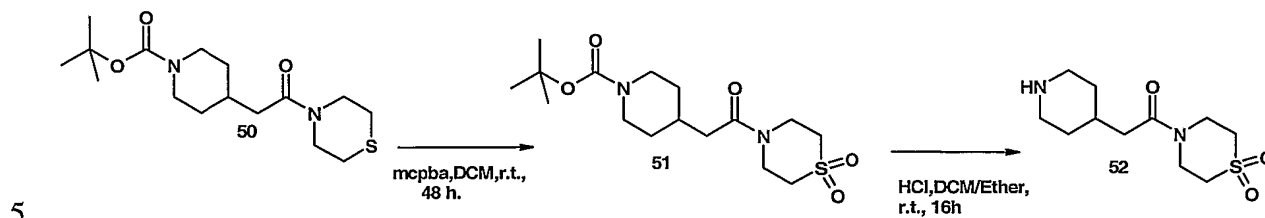
$^1H$  NMR ( $DMSO-d_6$ ) 0.97-1.16 (m, 2H), 1.50 (s, 9H), 1.70-1.88 (m, 3H), 2.29 (d, 2H), 2.73-2.92 (m, 2H), 2.99 (s, 2H), 3.23 (m, 2H), 3.40 (s, 2H), 4.00 and 4.04 (2s, 2H), 7.80 (s, 1H).

25 4.0M HCl in dioxane (10 ml, 40mmol) was added to a solution of **48** (0.2g, 0.67 mmol) in dioxane (40 ml) and the mixture stirred for 72h under an atmosphere of nitrogen. The dioxane was evaporated under reduced pressure to give a gummy solid. This was stirred with  $Et_2O$  for 3h and the resultant white solid isolated by centrifugation and dried to give **49** (0.156g).

MS-ESI: 198 ( $M^+ + H$ ).

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<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.42-1.60 (m, 2H), 2.22-2.35 (m, 3H), 2.97 (t, 2H), 3.18 (d, 2H), 3.36 and 3.40 (2s, 2H), 3.38-4.00 (m, 6H).

52 for Example 6.19

A mixture of **50** (1.5g, 4.57mmol) [see intermediate for Example 6.21] and MCPBA (70 %)(2.25g, 9.14mmol) in DCM (50ml) was stirred under a nitrogen atmosphere for 48h. It was then washed with sat. sodium bicarbonate solution(2x50ml), dried and evaporated to dryness under reduced pressure. The residue was washed with Et<sub>2</sub>O and dried to give **51** (1.65g) as a white solid.

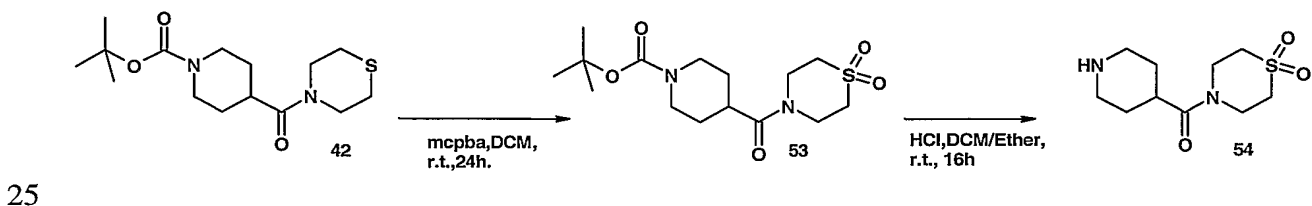
MS-ESI: 361 (M<sup>+</sup>+H).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.06-1.24 (m, 2H), 1.50 (s, 9H), 1.68-1.80 (m, 2H), 1.90-2.06 (m, 1H), 2.44 (d, 2H), 2.70-2.92 (m, 2H), 3.18 (m, 2H), 3.30 (m, 2H), 3.90-4.08 (m, 6H).

15 A 1.0M solution of HCl in Et<sub>2</sub>O (19.4 ml, 19.4mmol) was added to a solution of **51** (1.4g, 3.9mmol) in DCM (60ml) and the mixture stirred for 16h under a nitrogen atmosphere. The white precipitate was filtered, washed with Et<sub>2</sub>O and dried to give **52** (0.96g).

MS-ESI: 261 (M<sup>+</sup>+H).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.40-1.60 (m, 2H), 1.86-2.00 (m, 2H), 2.00-2.20 (m, 1H), 2.50 (d, 2H), 2.88-3.05 (q, 2H), 3.20 (m, 2H), 3.24-3.40 (m, 2H), 3.56 (m, 2H), 3.97 (m, 4H), 8.95 (br s, 1H), 9.02 (br s, 1H).

54 for Example 6.20

A mixture of **42** (1g, 3.18mmol) [see intermediate for Example 6.15] and MCPBA (70 %)(1.65g, 6.7mmol) in DCM (75ml) was stirred under a nitrogen atmosphere for 72h. It was then washed with sat. sodium bicarbonate solution(2 x 50ml), dried and evaporated to dryness

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under reduced pressure. The residue was washed with Et<sub>2</sub>O and dried to give **53** (1g) as a white solid.

MS-ESI: 369 (M<sup>+</sup>+Na).

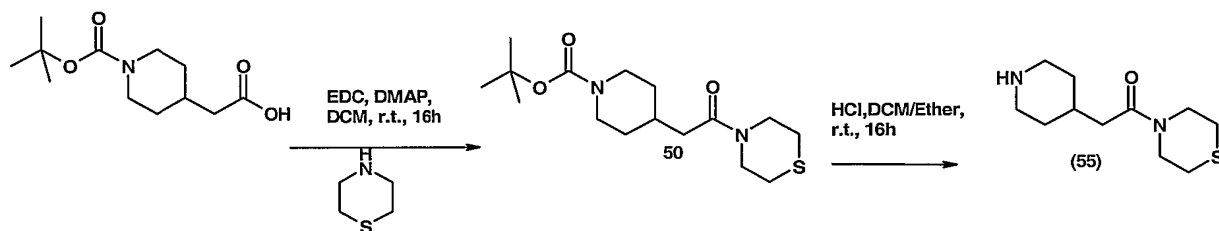
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.29-1.52 (m, 2H), 1.45 (s, 9H), 1.55-1.72 (m, 2H), 2.64-2.96 (m, 3H),  
5 3.00-3.28 (m, 4H), 3.72-4.00 (m, 6H).

A 1.0M solution of HCl in Et<sub>2</sub>O (10 ml, 10mmol) was added to a solution of **53** (1g, 2.9mmol) in DCM (80ml) and the mixture stirred for 16h under a nitrogen atmosphere. The white precipitate was filtered, washed with Et<sub>2</sub>O and dried to give **54** (0.65g).

10 MS-ESI: 247 (M<sup>+</sup>+H).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.75-2.00 (m, 4H), 2.91-3.45 (m, 9H), 3.91 (m, 4H), 8.80 (br s, 1H), 9.10 (br s, 1H).

(55) for Example 6.21



15

A mixture of N-Boc-4-piperidine-acetic acid (2.0g, 8.2 mmol), thiomorpholine (1g, 9.7mmol), DMAP (4.0g, 32.8 mmol) and EDC (2.0g, 10.4mmol) in dichloromethane (80 ml) was stirred under a nitrogen atmosphere for 16h. The reaction mixture was washed with a 1.0M aq. citric acid solution (2 x 50ml), sat.sodium bicarbonate solution, the organics separated, dried and  
20 evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography on silica eluting with 50-80%EtOAc/iso-hexane to give **50** (2.1g) as a white solid.

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.03-1.22 (m, 2H), 1.46 (s, 9H), 1.67-1.80 (m, 2H), 1.90-2.05 (m, 1H), 2.22 (d, 2H), 2.58-2.64 (m, 4H), 2.74 (t, 2H), 3.75 (t, 2H), 3.90 (t, 2H), 4.00-4.20 (m, 2H).

25

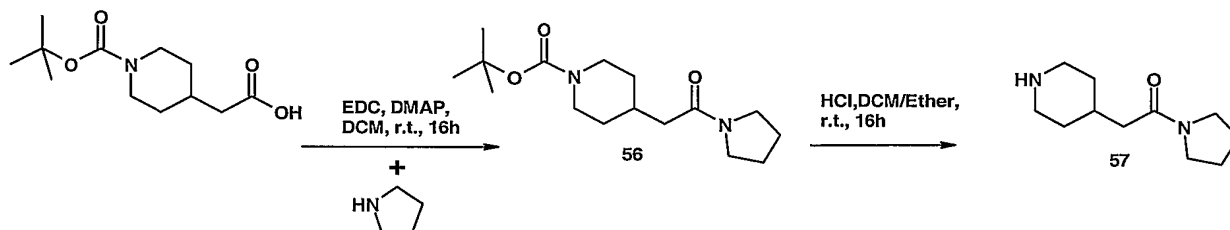
A 1.0M solution of HCl in Et<sub>2</sub>O (10 ml, 10mmol) was added to a solution of **50** (0.5g, 1.5mmol) in DCM (30ml) and the mixture stirred for 16h under a nitrogen atmosphere. The white precipitate was filtered, washed with Et<sub>2</sub>O and dried to give **55** (0.33g).

MS-ESI: 229 (M<sup>+</sup>+H).

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<sup>1</sup>H NMR (DMSOd<sub>6</sub>) 1.40-1.60 (m, 2H), 1.84-2.00 (m, 2H), 2.00-2.20 (m, 1H), 2.40 (d, 2H), 2.55-2.68 (m, 2H), 2.68-2.78 (m, 2H), 2.82-3.04 (q, 2H), 3.20-3.40 (m, 2H), 3.80 (m, 4H), 8.97 (br s, 1H), 9.15 (br s, 1H).

5

**57 for Example 6.23**

A mixture of N-Boc-4-piperidine-acetic acid (1.0g, 4.1 mmol), pyrrolidine (0.38g, 5.3mmol),  
 10 DMAP (2.0g, 16.4 mmol) and EDC (1.0g, 5.2mmol) in dichloromethane (60 ml) was stirred under a nitrogen atmosphere for 16h. The reaction mixture was washed with a 1.0M aq. citric acid solution (2 x 50ml), sat.sodium bicarbonate solution, the organics separated, dried and evaporated to dryness under reduced pressure. The residue was triturated and washed with Et<sub>2</sub>O to give a white solid, **56** (1.15g).  
 15 <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.04-1.21 (m, 2H), 1.45 (s, 9H), 1.68-1.79 (m, 2H), 1.80-2.13 (m, 5H), 2.18 (d, 2H), 2.72 (t, 2H), 3.40 (t, 2H), 3.46 (t, 2H), 3.98-4.20 (m, 2H).

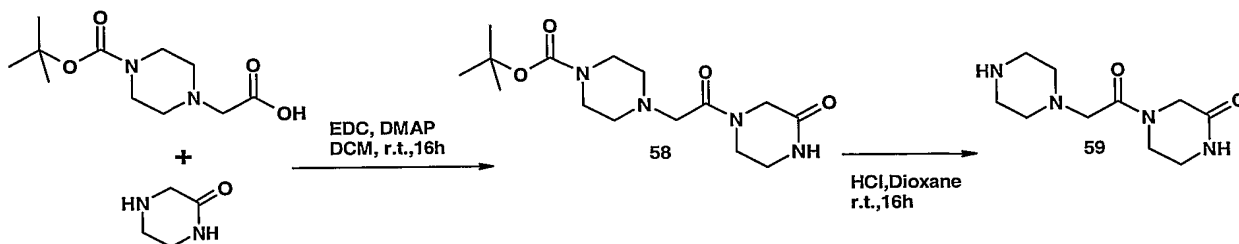
A 1.0M solution of HCl in Et<sub>2</sub>O (20 ml, 20mmol) was added to a solution of **56** (1g, 3.6mmol) in DCM (50ml) and the mixture stirred for 16h under a nitrogen atmosphere. The  
 20 solvent was decanted and the gummy solid washed with Et<sub>2</sub>O and then stirred with more Et<sub>2</sub>O for 18h. The precipitate was filtered and dried to give **57** (0.7g) as a white solid.

**MS-ESI:** 197 (M<sup>+</sup>+H).

<sup>1</sup>H NMR (DMSOd<sub>6</sub>) 1.40-1.60 (m, 2H), 1.80-2.02 (m, 6H), 2.02-2.20 (m, 1H), 2.30 (d, 2H), 2.94 (q, 2H), 3.20-3.32 (m, 2H), 3.37 (t, 2H), 3.48 (t, 2H), 9.00 (br s, 1H), 9.20 (br s, 1H).

25

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**59 for Example 6.24**

A mixture of N-Boc-piperazine acetic acid (0.5g, 2.05 mmol), piperazin-2-one (0.3g, 3.075mmol), DMAP (1.25g, 10.23 mmol) and EDC (0.51g, 2.7mmol) in dichloromethane (40 ml) was stirred under a nitrogen atmosphere for 16h. The reaction mixture was washed with a 1.0M aq. citric acid solution and the organics separated, dried and evaporated to dryness under reduced pressure. The residue was purified by flash column chromatography on silica eluting with EtOAc- 20%MeOH/EtOAc to give **58** as a solid foam (0.38g).

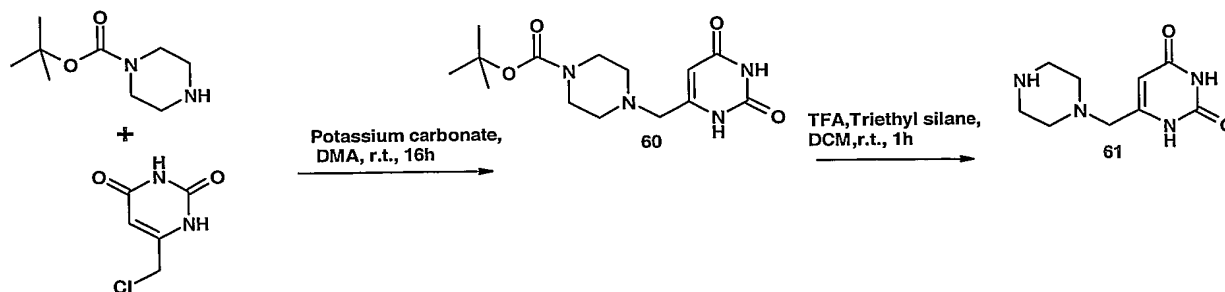
10 MS-ESI: 327 ( $M^+ + H$ ).

$^1H$  NMR ( $DMSO-d_6$ ) 1.50 (s, 9H), 2.48 (t, 4H), 3.20-3.48 (m, 8H), 3.70 and 3.80 (2t, 2H), 4.02 and 4.25 (2s, 2H), 8.12 (s, 1H).

4.0M HCl in dioxane (10 ml, 40mmol) was added to a solution of **58** (0.34g, 0.094mmol) in dioxane (50 ml) and the mixture stirred for 16h under an atmosphere of nitrogen. The dioxane was evaporated under reduced pressure to give a gummy solid. This was stirred with  $Et_2O$  for 3h and the resultant white solid isolated by centrifugation and dried to give **59** (0.224g).

MS-ESI: 227 ( $M^+ + H$ ).

$^1H$  NMR ( $DMSO-d_6$ ) 3.26-3.80 (m, 12H), 4.10 (d, 2H), 4.57 (s, 1H), 4.64 (s, 1H), 8.30 (d, 1H), 10.22 (br s, 2H), 3.34-3.55.

**61 for Example 6.25**

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A mixture of 1-Boc-piperazine (1.0g, 5.4mmol), 6-chloromethyluracil(0.9g, 5.6mmol) and potassium carbonate (1.5g, 10.9mmol) in DMA (50ml) was stirred at ambient temperature for 16h under a nitrogen atmosphere. The DMA was evaporated away under reduced pressure and the residue was stirred with water (30ml) and acidified with 1.0M aq. citric acid to pH 6-

- 5 7. The resulting white solid precipitate was filtered and dried to give **60** (1.0g).

MS-ESI: 311 ( $M^+ + H$ ).

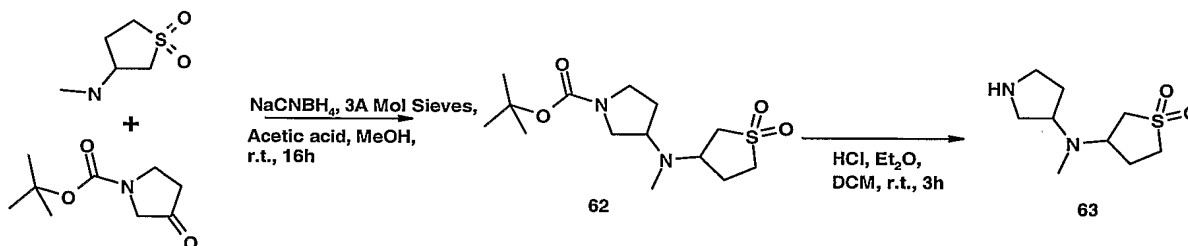
$^1H$  NMR (DMSO- $d_6$ ) 1.38 (s, 9H), 2.35 (t, 4H), 3.18 (s, 2H), 3.24-3.45 (m, 4H), 5.47 (s, 1H), 10.64 (br s, 1H), 10.91 (br s, 1H).

- 10 Triethylsilane (1.0ml, 12mmol) and then TFA (40ml) was added to a stirred suspension of **60** (0.55g, 1.8mmol) in DCM(10ml). under a nitrogen atmosphere. It was then stirred at ambient temperature for 1h. The TFA and DCM were evaporated away under reduced pressure and the residue washed with Et<sub>2</sub>O and dried to give **61** (0.5g) as a cream solid.

MS-ESI: 211 ( $M^+ + H$ ).

- 15  $^1H$  NMR (DMSO- $d_6$ ) 2.61 (t, 4H), 3.10 (m, 4H), 3.20 (s, 2H), 5.50 (s, 1H), 8.60 (br s, 2H), 10.65 (br s, 1H), 10.94 (br s, 1H).

**63** for Example 6.26



- 20 Glacial acetic acid (230μl, 4.02 mmol) was added drop-wise to a stirred solution of N-Boc-3-pyrrolidinone (0.3g; 1.62 mmol), 3-methylamino-tetrahydrothiophene-1-dioxide hydrochloride (0.15g, 0.81 mmol), sodium cyanoborohydride (0.102g, 1.62mmol), and 3A molecular sieves (0.3g) in MeOH (3 ml) at ambient temperature under nitrogen. After stirring for 16h the reaction mixture was filtered through a pad of celite and the filtrate evaporated to dryness under reduced pressure. The residue was partitioned between DCM (30ml) and sat. NaHCO<sub>3</sub> (20ml), the organics were separated and further washed with sat.brine (20ml), dried and evaporated to dryness. The residue was by chromatography on silica, eluting with 80% EtOAc/DCM then 2-5% MeOH/DCM to give **62** as a white solid (0.16g).

MS-ESI: 319 ( $M^+ + H$ ).

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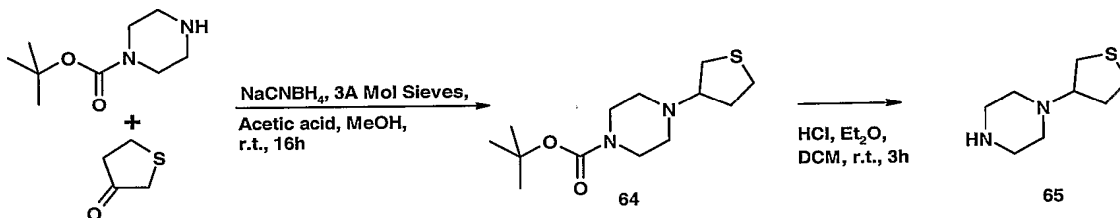
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.47 (s, 9H), 1.70-1.90 (m, 1H), 1.95-2.10 (m, 1H), 2.12-2.40 (m, 5H), 2.90-3.35 (m, 7H), 3.40-3.73 (m, 3H).

1.0M HCl in Et<sub>2</sub>O (2.5ml, 2.5 mmol) and conc HCl (0.5ml) were added to a solution of **62** (0.16g, 0.50 mmol) in DCM (3ml). After stirring at ambient temperature for 3h the solvents were evaporated under reduced pressure to give **63** as a yellow solid (0.128g).

MS-ESI: 219 (M<sup>+</sup>+H).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 2.10-2.40 (m, 17H), 9.73 (s, 1H).

# **65 for Example 6.27**



Glacial acetic acid (1.54ml, 26.9 mmol) was added dropwise to a stirred solution of N-Boc-piperazine (1.0g, 5.38 mmol), tetrahydro-thiophene-3-one (919μl, 10.76 mmol), sodium cyanoborohydride (0.677g, 10.75 mmol) and 3A molecular sieves (2.0g) in MeOH (20ml) at ambient temperature under nitrogen. After stirring for 16h the reaction mixture was filtered through a pad of celite and the filtrate evaporated to dryness under reduced pressure. The residue was partitioned between DCM (50ml) and sat. NaHCO<sub>3</sub> (30ml), the organics were separated and further washed with sat. brine (30ml), dried and evaporated to dryness. The residue was purified by chromatography on silica, eluting with 10-40% EtOAc/DCM to give **64** as a white solid (0.74g).

MS-ESI: 273 (M<sup>+</sup>+H).

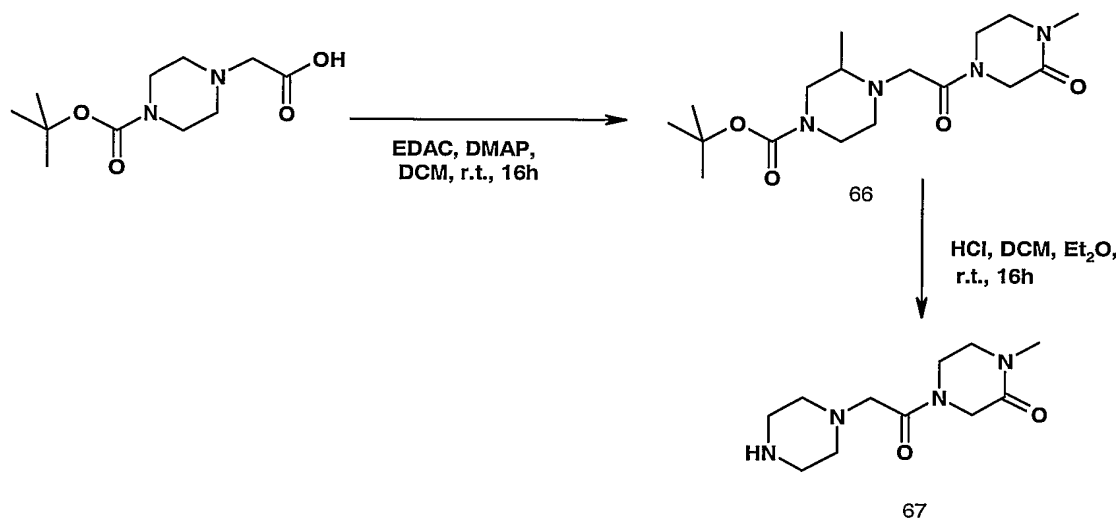
<sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.45 (s, 9H), 1.75-1.90 (m, 1H), 2.20-2.32 (m, 1H), 2.40-2.60 (m, 4H), 2.65-2.79 (m, 1H), 2.80-3.00 (m, 4H), 3.34-3.55 (m, 4H).

1.0M HCl in Et<sub>2</sub>O (6.8ml, 6.8 mmol) and conc HCl (0.5ml) were added to a solution of **64** (0.37g, 1.36 mmol) in DCM (2ml). After stirring at ambient temperature for 3h the solvents were evaporated away to give **65** as a yellow solid (0.283g).

MS-ESI: 173 (M<sup>+</sup>+H).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 2.00-2.25 (m, 2H), 2.75-4.00 (m, 13H), 9.65 (br s, 1H).

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67 for Example 6.28

- 5 A mixture of N-Boc-4-piperazine-acetic acid hydrochloride dihydrate (0.4g, 1.26 mmol), N-methyl-2-piperazinone (0.194g, 1.7mmol), DMAP (1.0g, 8.2 mmol) and EDC (0.4g, 2.1mmol) in dichloromethane (60 ml) was stirred under a nitrogen atmosphere for 16h. The reaction mixture was washed with a 1.0M aq. citric acid solution (2 x 50ml), sat.sodium bicarbonate solution, the organics separated, dried and evaporated to dryness under reduced
- 10 pressure. The residue was purified by chromatography on silica eluting with 10-20%MEOH/EtOAc to give **66** (0.3g) as a solid foam.

MS-ESI: 341 ( $M^+ + H$ ).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.50 (s, 9H), 2.48 (m, 4H), 2.97 (s, 3H), 3.22-3.56 (m, 8H), 3.78 & 3.90 (2t, 2H), 4.09 & 4.29 (2s, 2H).

15

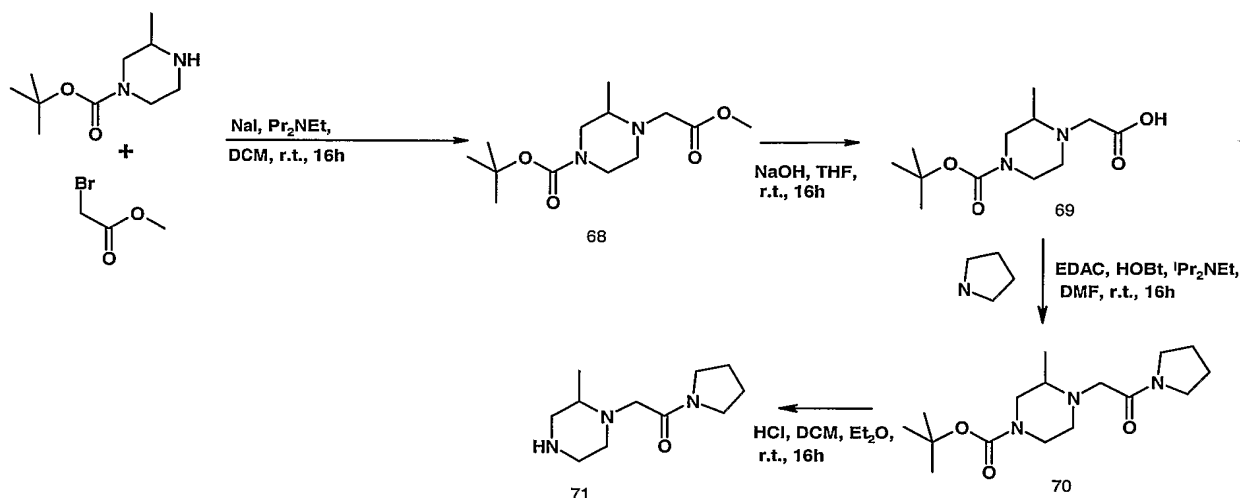
A 1.0M solution of HCl in Et<sub>2</sub>O (7.6 ml, 7.6mmol) was added to a solution of **66** (0.26g, 0.76mmol) in DCM (50ml) and the mixture stirred for 16h under a nitrogen atmosphere. The precipitate was filtered, washed with Et<sub>2</sub>O and dried to give **67** (0.145g) as a white solid.

MS-ESI: 241 ( $M^+ + H$ ).

- 20 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 3.00 (s, 3H), 3.36-3.89 (m, 12H), 4.15 (s, 2H), 4.54 & 4.62 (2s, 2H), 10.08-10.25 (v.br s, 2H).



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71 for Example 6.29

Methyl-bromoacetate (3.06g, 20.0 mmol) was added to a stirred solution of 4-Boc-2-methyl-  
 5 piperazine (2.0g, 10.0 mmol), sodium iodide (0.1g.) and N,N-diisopropylethylamine (3.48 ml, 20 mmol) in DCM (50ml) at ambient temperature under nitrogen. After stirring for 16h the reaction mixture was washed with water (30ml), brine (30ml), dried and evaporated to dryness under reduced pressure. The residue was purified by chromatography on silica, eluting with 0-8% MeOH/DCM to give **68** as a yellow oil (2.7g).

10 MS-ESI: 273 ( $\text{M}^+\text{+H}$ ).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.05 (d, 3H), 1.47 (s, 9H), 2.50-2.85 (m, 4H), 3.03-3.13 (m, 1H), 3.34 (d, 1H), 3.44 (d, 1H), 3.70 (s, 3H), 3.71-3.82 (m, 2H).

2.0M NaOH (25ml, 49.6 mmol) was added to a solution of **68** (2.7g, 9.9 mmol) in THF  
 15 (150ml). After stirring at ambient temperature for 72h the reaction mixture was adjusted to pH7 with 2N HCl and the solvents were evaporated. The residue was partitioned between water and EtOAc, the organics separated, dried and evaporated to dryness to give **69** as a yellow solid (2.56g).

MS-ESI: 259 ( $\text{M}^+\text{+H}$ ).

20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 0.93 (d, 3H), 1.35 (s, 9H), 2.40-2.80 (m, 4H), 2.86-3.02 (m, 1H), 3.15 (d, 1H), 3.25 (d, 1H), 3.50-3.70 (m, 2H).

A mixture of **69** (1.28g, 5.0 mmol), pyrrolidine (829 $\mu\text{l}$ , 9.9mmol), HOBT (1.0g, 7.4 mmol) and EDC (1.7g, 8.9mmol) in DMF (30 ml) was stirred under a nitrogen atmosphere for 16h. The

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reaction mixture was evaporated under reduced pressure and the residue was partitioned between DCM (50ml) and water (50ml). The organic phase was washed with brine (20ml), dried and evaporated to dryness. The residue was purified by chromatography on silica, eluting with 0-5% MeOH/DCM to give **70** as a yellow oil (0.904g).

5 MS-ESI: 312 ( $M^+ + H$ ).

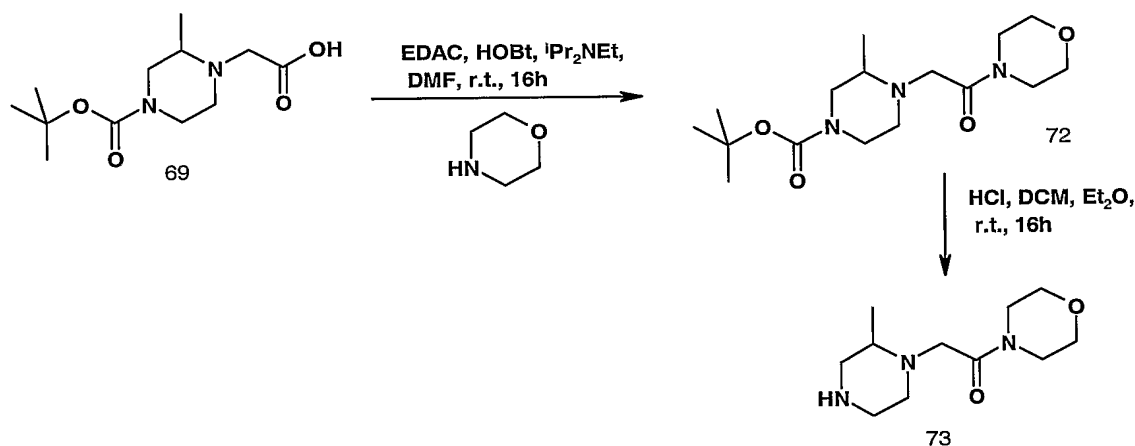
$^1H$  NMR ( $CDCl_3$ ) 1.05 (d, 3H), 1.45 (s, 9H), 1.75-2.02 (m, 5H), 2.38-2.50 (m, 1H), 2.52-2.66 (m, 1H), 2.70-2.80 (m, 2H), 3.02 (d, 1H), 3.09-3.20 (m, 1H), 3.37-3.60 (m, 5H), 3.62-3.80 (m, 1H).

10 10N HCl (0.9 ml, 29mmol) was added to a solution of **70** (0.9g, 2.9mmol) in DCM (3ml) and  $Et_2O$  (10ml) and the mixture stirred for 16h at ambient temperature. The solvents were evaporated and further azeotroped with toluene before triturating with MeOH/ $Et_2O$  to give **71** as a white solid (0.42g).

MS-ESI: 212 ( $M^+ + H$ ).

15  $^1H$  NMR ( $DMSO-d_6$ ) 1.00-1.35 (m, 3H), 1.68-1.97(m, 4H), 2.80-3.80 (m, 13H).

**73** for Example 6.30



A mixture of **69** (1.28g, 5.0 mmol), morpholine (872 $\mu$ l, 9.9mmol),  $DIPEA$  (2.58g, 20mmol),  
 20 HOBt (1.0g, 7.4 mmol) and EDC (1.7g, 8.9mmol) in DMF (30 ml) was stirred under a nitrogen atmosphere for 16h. The reaction mixture was evaporated and the residue was partitioned between DCM (50ml) and water (50ml). The organic phase was washed with brine (20ml), dried and evaporated to dryness under reduced pressure. The residue was purified by chromatography on silica, eluting with 0-5% MeOH/DCM to give **72** as a yellow oil (1.28g).

25 MS-ESI: 328.2 ( $M^+ + H$ ).

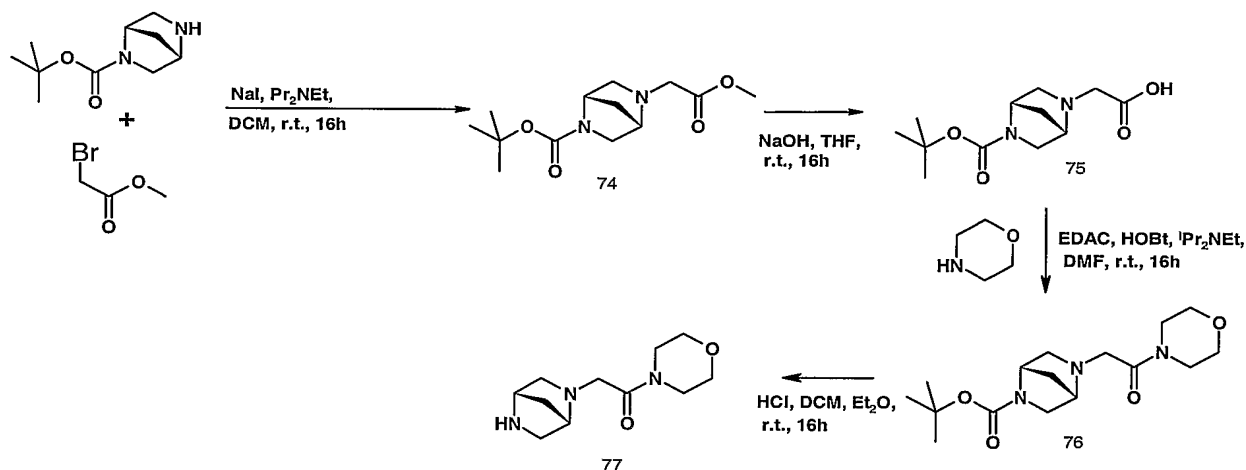
## - 114 -

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.05 (d, 3H), 1.48 (s, 9H), 2.30-2.40 (m, 1H), 2.41-2.55 (m, 1H), 2.70-2.80 (m, 1H), 2.95-3.07 (m, 1H), 3.10-3.20 (m, 1H), 3.40-3.83 (m, 12H).

10N HCl (0.6 ml, 20mmol) was added to a solution of **72** (1.28g, 3.9mmol) in DCM (3ml) and EtO<sub>2</sub> (10ml) and the mixture stirred for 16h at ambient temperature. The solvents were evaporated and azeotroped with toluene before triturating with MeOH/Et<sub>2</sub>O to give **73** as a white solid (0.77g).

MS-ESI: 228 (M<sup>+</sup>+H).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.20-1.44 (m, 3H), 3.20-3.75 (m, 14H), 3.83-4.03 (m, 1H), 4.30-4.60 (m, 2H).

**77 for Example 6.31**

Methyl-bromo-acetate (771mg, 5.0 mmol) was added to a stirred solution of *tert*-butyl (1S,4S)-(-)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (0.5g, 2.5 mmol), sodium iodide (0.1g.) and N,N-diisopropylethyl amine (1.32 ml, 7.6 mmol) in DCM (10ml) at ambient temperature under nitrogen. After stirring for 16h the reaction mixture was washed with water (30ml), brine (30ml), dried and evaporated to dryness. The residue was purified by chromatography on silica, eluting with 0-5% MeOH/DCM to give **74** as a yellow oil (0.25g).

MS-ESI: 271 (M<sup>+</sup>+H).

2.0M NaOH (2.3ml, 4.6 mmol) was added to a solution of **74** (0.25g, 0.9 mmol) in THF (3ml). After stirring at ambient temperature for 24h, the reaction mixture was adjusted to pH7 with 2N HCl and the solvents were evaporated off. The residue was partitioned between water

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and EtOAc, the organics separated, dried and evaporated to dryness to give **75** as a yellow solid (0.238g).

MS-ESI: 257 ( $M^+ + H$ ).

- 5 A mixture of **75** (0.119g, 0.5 mmol), morpholine (82 $\mu$ l, 0.9mmol), HOBt (0.095g, 0.7 mmol), DIPEA (0.26g, 2.0mmol) and EDC (0.161g, 0.8mmol) in DMF (5 ml) was stirred under a nitrogen atmosphere for 16h. The reaction mixture was evaporated and the residue was partitioned between DCM (20ml) and water (10ml). The organic phase was washed with brine (10ml), dried and evaporated to dryness under reduced pressure. The residue was purified by
- 10 chromatography on silica, eluting with 0-5% MeOH/DCM to give **76** as a yellow oil (0.03g).

MS-ESI: 326 ( $M^+ + H$ ).

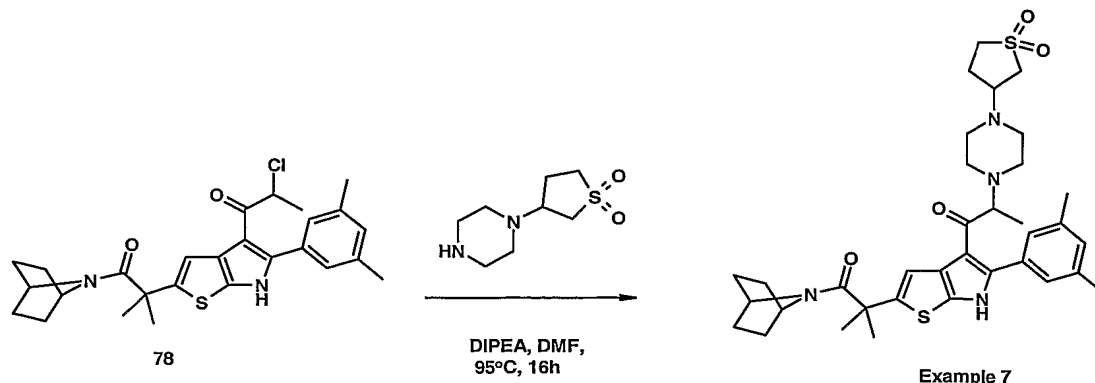
$^1H$  NMR ( $CDCl_3$ ) 1.48 (s, 9H), 1.64-1.97 (m, 2H), 2.54-2.80 (m, 1H), 2.87-3.10 (m, 1H), 3.12-3.28 (m, 1H), 3.30-3.80 (m, 12H), 4.30 (d, 1H).

- 15 2N HCl in  $Et_2O$  (460  $\mu$ l, 0.9mmol) was added to a solution of **76** (0.03g, 0.09mmol) in DCM (0.5ml) and stirred for 16h at ambient temperature. The solvents were evaporated to give **77** as a yellow glass (0.024g).

MS-ESI: 226 ( $M^+ + H$ ).

## 20 Example 7

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[1-oxo-2-methyl-2-{4-(1,1-dioxidotetrahydro-3-thienyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrole**



- 25 1-( tetrahydro-1,1-dioxido-3-thienyl)-piperazine (0.084g, 0.41 mmol) was added to a stirred solution of **78** (0.1g, 0.21 mmol), catalytic NaI and diisopropyl ethyl amine (180 $\mu$ l, 1.04

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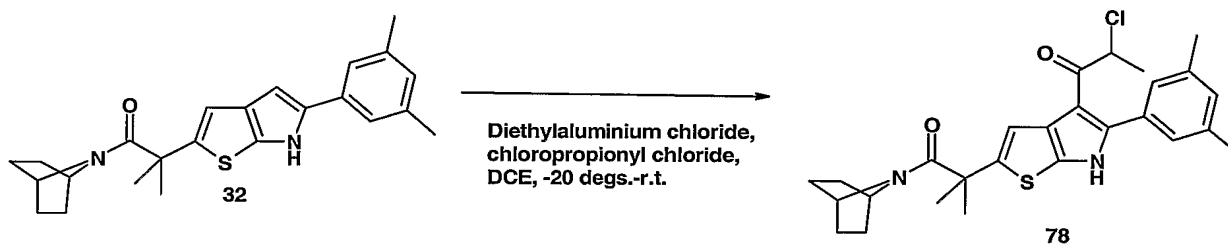
mmol) in DMF (3ml). After stirring for 16h at 90°C under N<sub>2</sub> the reaction mixture was evaporated to dryness under reduced pressure. The residue was partitioned between DCM (10ml) and water (5ml), the organics separated, washed with brine (5ml), dried and evaporated to dryness. The crude product was purified by chromatography on silica, eluting  
5 with 0-4% MeOH/DCM to give Example 7 as a yellow solid foam (0.068g).

Yield: 51%

MS-ESI: 651 (M<sup>+</sup>+H).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.18 (d, 3H), 1.20-1.40 (m, 4H), 1.45-1.80 (m, 10H), 1.98-2.13 (m, 1H),  
2.25-2.65 (m, 15H), 2.85-3.10 (m, 2H), 3.11-3.30 (m, 3H), 3.70-3.80 (m, 1H), 4.00-5.00 (m,  
10 2H), 7.06 (s, 1H), 7.12 (s, 2H), 7.20 (s, 1H), 8.98 (s, 1H)

Synthesis of 78



15 **78** was prepared in a similar manner to the synthesis of **31** using 2-chloropropionyl chloride instead of chloroacetyl chloride and DCE instead of DCM (see Example 6).

MS-ESI: 482.95, 484.91 (M<sup>+</sup>+H).

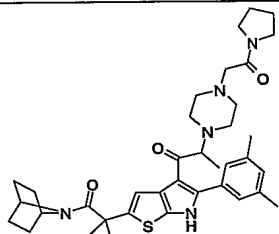
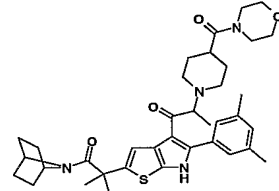
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.2-1.6 (m, 8H), 1.50 and 1.52 (2s, 6H), 1.54 (d, 3H), 2.32 (s, 6H), 4.12-  
4.40 (m, 2H), 5.00 (q, 1H), 7.08 (s, 1H), 7.10 (s, 1H), 7.20 (s, 2H), 12.40 (br s, 1H).

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**Examples 7.1-7.2**

Following a procedure similar to that described in Example 7, the compounds of table 7 were prepared.

**Table 7**

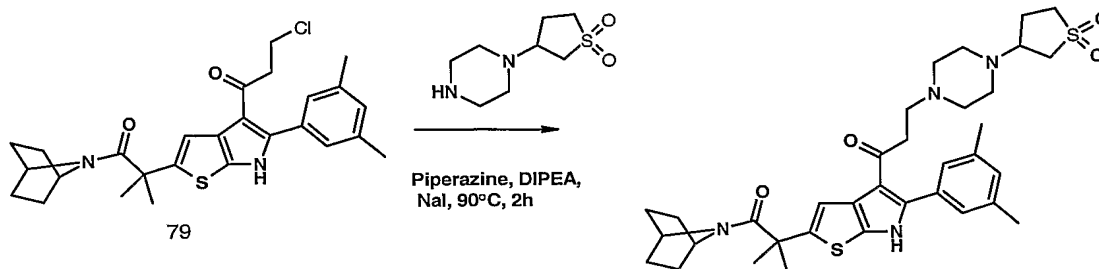
Example	Structure	<sup>1</sup> H NMR (CDCl <sub>3</sub> )	MS-ESI: (M <sup>+</sup> +H)
7.1		1.17 (d, 3H), 1.20-1.38 (m, 4H), 1.44-1.73 (m, 10H), 1.75-2.04 (m, 4H), 2.34 (s, 6H), 2.38-2.65 (m, 8H), 3.34-3.53 (m, 4H), 3.54-3.66 (m, 2H), 3.70-3.80 (m, 1H), 4.00-5.00 (m, 2H), 7.05 (s, 1H), 7.14 (s, 2H), 7.21 (s, 1H), 9.64 (s, 1H)	644
7.2		1.05-1.38 (m, 8H), 1.40-1.80(m, 17H), 2.35 (s, 6H), 3.35-3.75 (m, 10H), 4.00-5.00 (m, 2H), 7.05 (s, 1H), 7.16 (s, 2H), 7.24 (s, 1H), 9.07(s, 1H)	645

5

For the synthesis of the side-chain intermediates the reader is referred to Example 6.3 for Example 7.1 and Example 6.13 for Example 7.2.

**Example 8.**

- 10 **2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[1-oxo-3-{4-(1,1-dioxidotetrahydro-3-thienyl)piperazin-1-yl}propyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrole**

**Example 8**

Example 8 was prepared using the method in Example 6 and 79 instead of 31.

- 15 MS-ESI: 651 (M<sup>+</sup>+H).

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The starting material **79** was prepared from **32** using the procedure in the preparation of **31** and 3-chloropropionyl chloride instead of chloroacetyl chloride.

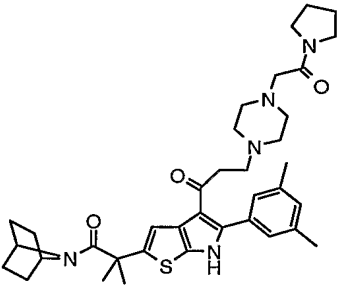
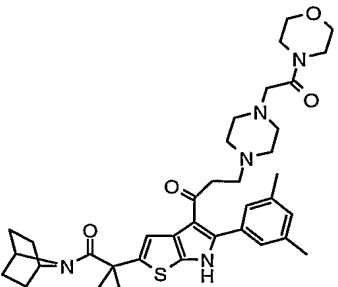
MS-ESI: 482.92, 484.90 ( $M^+ + H$ ).

- 5  $^1H$  NMR ( $DMSO-d_6$ ) 1.2-1.6 (m, 8H), 1.57 (s, 6H), 2.33 (s, 6H), 3.05 (t, 2H), 3.82 (t, 2H), 4.02-4.39 (m, 2H), 7.06 (s, 1H), 7.09 (s, 1H), 7.20 (s, 2H), 12.21 (br s, 1H).

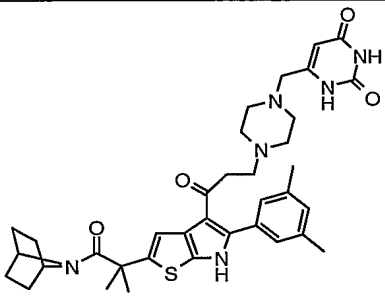
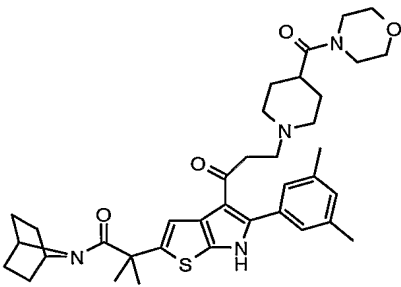
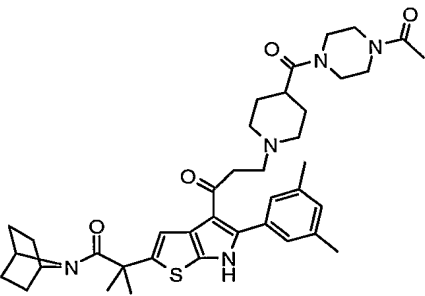
### Examples 8.1-8.5

Following a procedure similar to that described in Example 8, the compounds of table 8 were  
10 prepared.

**Table 8**

Example	Structure	$^1H$ NMR ( $DMSO-d_6$ )	MS-ESI: ( $M^+ + H$ )
8.1		1.20-1.60 (m, 8H), 1.53 (s, 6H), 1.65-1.94 (m, 4H), 2.20-2.80 (m, 12H), 2.30 (s, 6H), 3.00-3.48 (m, 4H), 3.29 (s, 2H), 4.10-4.40 (m, 2H), 7.04 (s, 1H), 7.08 (s, 1H), 7.18 (s, 2H)	644
8.2		1.20-1.60 (m, 8H), 1.53 (s, 6H), 2.10-2.80 (m, 10H), 2.32 (s, 6H), 3.00-3.16 (m, 2H), 3.21-3.60 (m, 8H), 3.28 (s, 2H), 4.10-4.40 (m, 2H), 7.05 (s, 1H), 7.08 (s, 1H), 7.18 (s, 2H), 12.15 (br s, 1H)	660

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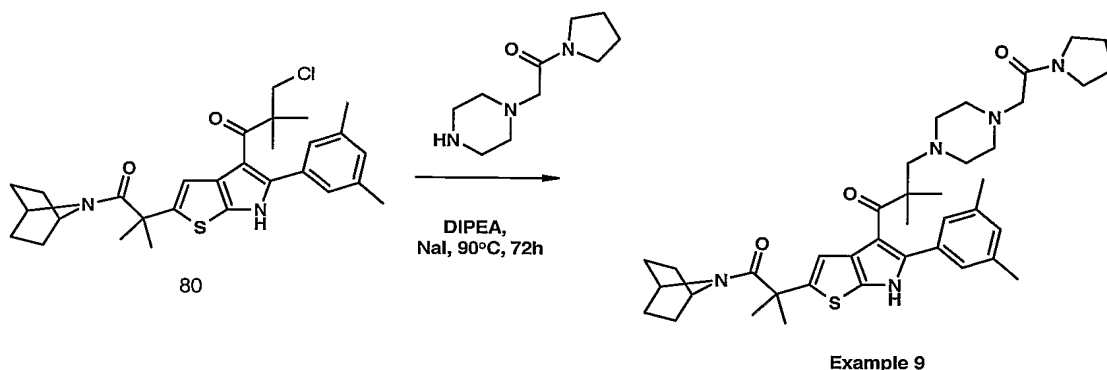
Example	Structure	<sup>1</sup> H NMR (DMSO-d <sub>6</sub> )	MS-ESI: (M <sup>+</sup> +H)
8.3		1.20-1.60 (m, 8H), 1.53 (s, 6H), 2.10-2.64 (m, 8H), 2.32 (s, 6H), 2.64-2.73 (m, 2H), 3.04-3.20 (m, 2H), 3.28 (s, 2H), 4.10-4.50 (m, 2H), 5.41 (br s, 1H), 7.05 (s, 1H), 7.08 (s, 1H), 7.19 (s, 2H)	657
8.4		1.00-1.40 (m, 8H), 1.40-1.63 (m, 2H), 1.54 (s, 6H), 1.63-1.89 (m, 2H), 2.20-2.60 (m, 8H), 2.32 (s, 6H), 2.80-3.00 (m, 1H), 3.00-3.70 (m, 8H), 4.10-4.50 (m, 2H), 7.06 (s, 1H), 7.09 (s, 1H), 7.22 (s, 2H)	645
8.5		1.20-1.37 (m, 4H), 1.37-1.60 (m, 6H), 1.53 (s, 6H), 1.79-1.94 (m, 2H), 2.00 (s, 3H), 2.25 & 2.43 (2m, 1H), 2.31 (s, 6H), 2.45-2.60 (m, 4H), 2.60-2.80 (m, 4H), 3.32-3.55 (m, 8H), 4.10-4.50 (m, 2H), 7.05 (s, 1H), 7.09 (s, 1H), 7.18 (s, 2H), 12.15 (br s, 1H)	686



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**Example 9.**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[1-oxo-2,2-di-methyl-3-{4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl}propyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**



5

Example **9** was prepared using the method in Example **6** and **80** instead of **31** and heating for 72h.

MS-ESI: 672 ( $M^+ + H$ ).

$^1H$  NMR ( $CDCl_3$ ) 1.08-1.75 (m, 8H), 1.18 (s, 6H), 1.73 (s, 6H), 1.75-2.00 (m, 4H), 2.32 (s, 6H), 2.20-2.75 (m, 12H), 3.05 (s, 2H), 3.38-3.55 (m, 2H), 4.10-4.80 (m, 2H), 6.92 (s, 1H), 6.96 (s, 1H), 7.09 (s, 2H), 8.54 (s, 1H).

10

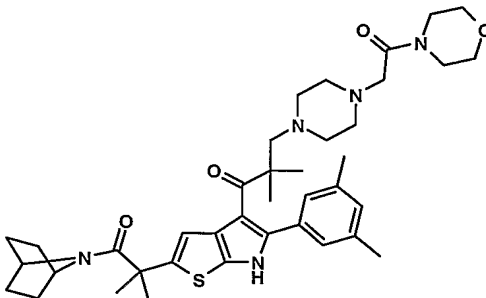
The starting material **80** was prepared from **32** using the procedure in the preparation of **31** with 3-chloropivaloyl chloride instead of chloroacetyl chloride.

15 MS-ESI: 511 ( $M^+ + H$ ).

$^1H$  NMR ( $DMSO-d_6$ ) 1.20 (s, 6H), 1.20-1.60 (m, 8H), 1.52 (s, 6H), 2.27 (s, 6H), 3.80 (s, 2H), 4.04-4.40 (m, 2H), 6.96 (s, 1H), 7.04 (s, 2H), 7.26 (s, 1H), 12.10 (br s, 1H).

Example **9.1** was synthesised by the procedure used to prepare Example **9** and the appropriate starting material:

20



Example 9.1

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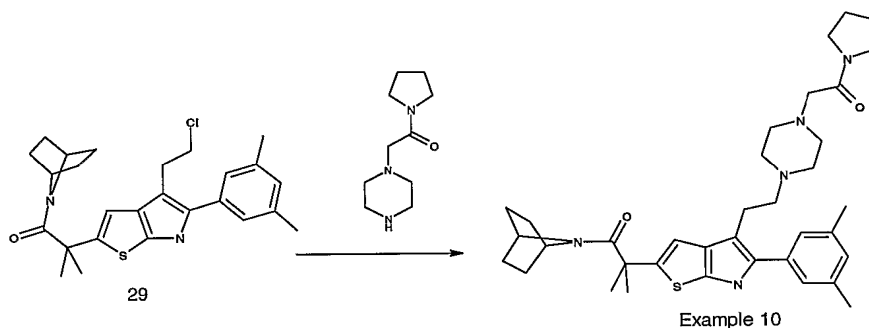
MS-ESI: 688 ( $M^+ + H$ ).

$^1H$  NMR (DMSO  $d_6$ ) 1.19-1.65 (m, 7H), 1.51 (s, 6H), 1.80-2.00 (m, 1H), 2.08-2.60 (m, 8H), 2.24 (s, 6H), 2.29 (s, 6H), 2.60-2.80 (m, 3H), 2.71 & 2.89 (2s, 2H), 2.80-2.95 (m, 1H), 2.95-3.40 (m, 6H), 4.09-4.45 (m, 2H), 7.04 (s, 1H), 7.08 (s, 1H), 7.17 (s, 2H), 12.13 (br s, 1H).

5

**Example 10**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-{4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**



10

A mixture of **29** (0.182 g; 0.4 mmol), N-(pyrrolidinocarbonylmethyl) piperazine (0.095 g, 0.48 mmol), NaI (0.072g; 0.48 mmol) and  $K_2CO_3$  (0.067 g; 0.48 mmol) in acetonitrile (4 ml) was heated at 80°C under argon atmosphere for 8 hours. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 2-5% of 3.5 N  $NH_3$  in MeOH /

15 methylene chloride to give after trituration in ether/pentane Example **10** as a solid.

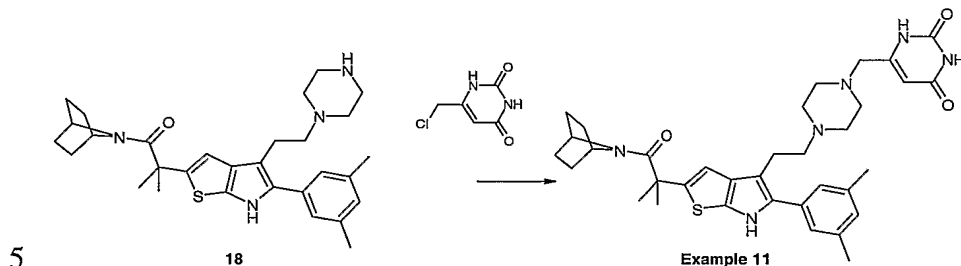
Yield: 42%

$^1H$  NMR ( $CDCl_3$ ) : 1.15-1.4 (m, 6H); 1.45-1.75 (m, 6H); 1.59 (s, 6H); 1.8-2 (m, 4H); 2.32 (s, 6H); 2.45-2.75 (m, 6H); 2.9-3 (m, 2H); 3.1 (s, 2H); 3.44-3.5 (m, 4H); 4-4.2 (m, br, 1H); 4.6-20 4.8 (m, br, 1H); 6.72 (s, 1H); 6.92 (s, 1H); 7.04 (s, 2H); 8.13 (s, 1H).

MS-ESI: 616  $[M+H]^+$

**Example 11**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-{4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-ylmethyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole**



A mixture of **18** (0.252 g; 0.5 mmol), 6-chloromethyluracil (0.088g; 0.55 mmol), K<sub>2</sub>CO<sub>3</sub> (0.076 g; 0.55 mmol) and NaI (0.082 g; 0.55 mmol) in acetonitrile (5 ml) was heated at 85°C under argon atmosphere for 4 hours. The mixture was purified by flash chromatography eluting with a gradient of 5-10 % MeOH / CH<sub>2</sub>Cl<sub>2</sub> to give **Example 11** as a solid.

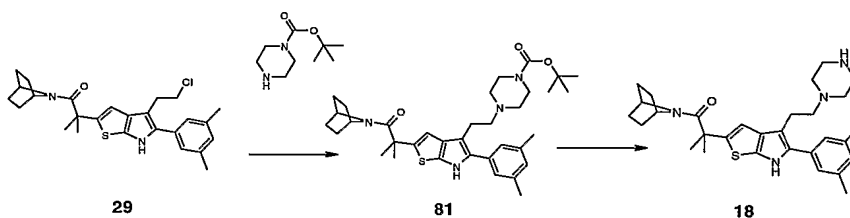
10 Yield: 63 %

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.2-1.4 (m, 4H); 1.6 (s, 6H); 1.4-1.8 (m, 4H); 2.34 (s, 6H); 2.4-2.7 (m, 10H); 2.85-2.95 (m, 2H); 3.3 (s, 2H); 4-4.2 (m, br, 1H); 4.6-4.8 (m, br, 1H); 5.53 (s, 1H); 6.72 (s, 1H); 6.93 (s, 1H); 7.04 (s, 2H); 8.05-8.2 (m, 2H).

MS-ESI: 629 [M+H]<sup>+</sup>

15

The starting material was prepared as follows:



A mixture of **29** (12.4 g; 0.027mol), N-(tert-butoxycarbonyl)piperazine (10.15g; 0.054 mol), K<sub>2</sub>CO<sub>3</sub> (7.52 g; 0.054 mol) in acetonitrile (120 ml) was heated at 85°C under argon atmosphere for 3 hours. The mixture was evaporated and purified by flash chromatography, eluting with a 50-100 gradient of ethyl acetate / petroleum ether to give **81**.

Yield: 94%

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.15-1.4 (m, 4H); 1.45-1.8 (m, 4H); 1.44 (s, 9H); 1.6 (s, 6H); 2.33 (s, 6H); 2.35-2.5 (m, 4H); 2.6-2.7 (m, 2H); 2.9-3 (m, 2H); 3.4-3.5 (m, 4H); 4.0-4.2 (m, br, 1H); 4.6-4.8 (m, br, 1H); 6.71 (s, 1H); 6.93 (s, 1H); 7.04 (s, 2H); 8.13 (s, 1H).

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To a solution of **81** (15.32g;0.025 mol) in methylene chloride (250ml) was added at 0°C TFA (95ml). After stirring at ambient temperature for 1 hour, the mixture was evaporated, treated with 3.5N NH<sub>3</sub> in MeOH ( 100ml) and purified by flash chromatography eluting with a 5-8% gradient of 3.5N NH<sub>3</sub> in MeOH / CH<sub>2</sub>Cl<sub>2</sub> to give after trituration with ether **18** as a solid.

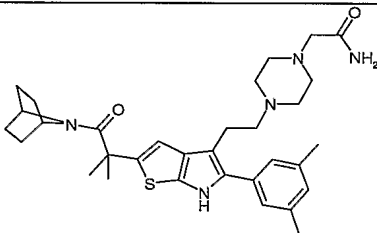
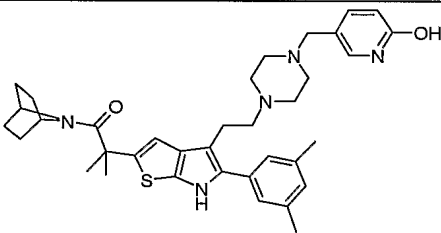
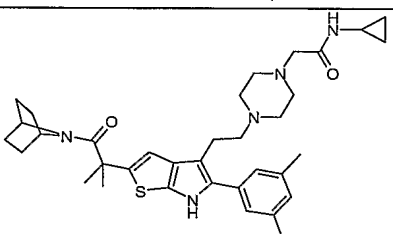
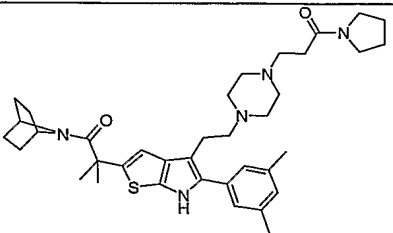
5 Yield : 95%

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.15-1.4 (m, 4H); 1.45-1.75 (m, 4H); 1.6 (s, 6H); 2.33 (s, 6H); 2.5 (m, 4H); 2.6-2.7 (m, 2H); 2.85-3 (m, 6H); 4.0-4.2 (m, br, 1H); 4.6-4.8 (m, br, 1H); 6.72 (s, 1H); 6.92 (s, 1H); 7.05 (s, 2H); 8.15 (s, 1H).

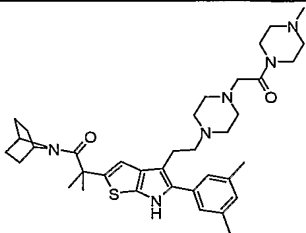
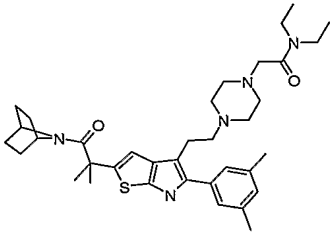
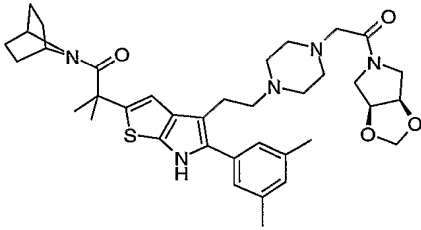
10 **Examples 11.1 –11.7**

Following a procedure similar to that described in **Example 11**, the compounds of table 11 were prepared.

**Table 11**

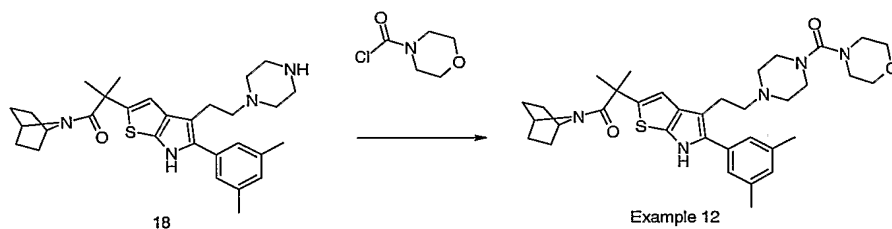
Example		MS-ESI
11.1		562 [M+H] <sup>+</sup>
11.2		612 [M+H] <sup>+</sup>
11.3		602 [M+H] <sup>+</sup>
11.4		630 [M+H] <sup>+</sup>

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Example		MS-ESI
11.5		645 [M+H] <sup>+</sup>
11.6		618 [M+H] <sup>+</sup>
11.7		660 [M+H] <sup>+</sup>

**Example 12**

2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-{4-(morpholinocarbonyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-5H-thieno[2,3-b]pyrrole



4-morpholinecarbonyl chloride (0.058g; 0.367 mmol) was added under argon atmosphere, at 0°C to a suspension of **18** (0.185g; 0.367 mmol) and triethylamine (0.054 ml; 0.385 mmol) in acetonitrile (4ml). The mixture was stirred at ambient temperature for 3 hours. After evaporation to dryness, the residue was purified by flash chromatography, eluting with a gradient 5-7% of 3.5N NH<sub>3</sub> in MeOH / methylene chloride to give after trituration in ether Example **12** as a solid.

Yield: 60%

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$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.15-1.4 (m, 4H); 1.6 (s, 6H); 2.45-2.8 (m, 4H); 2.33 (s, 6H); 2.47-2.50 (m, 4H); 2.6-2.7 (m, 2H); 2.9-3 (m, 2H); 3.15-3.4 (m, 8H); 3.6-3.7 (m, 4H); 4-4.2 (m, br, 1H); 4.6-4.8 (m, br, 1H); 6.7 (s, 1H); 6.93 (s, 1H); 7.03 (s, 2H); 8.13 (s, 1H).

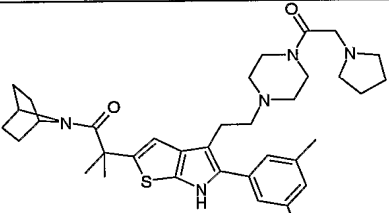
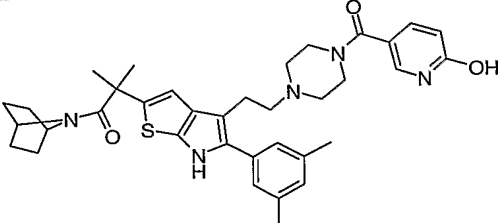
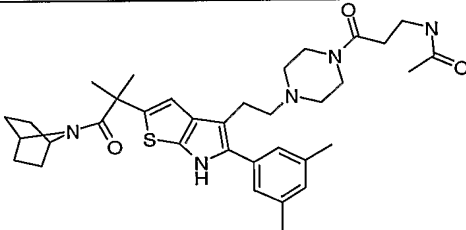
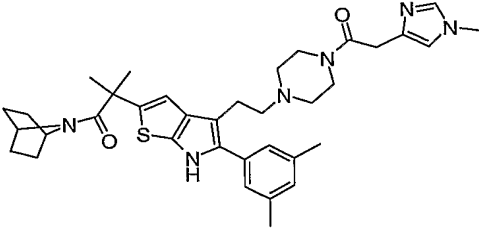
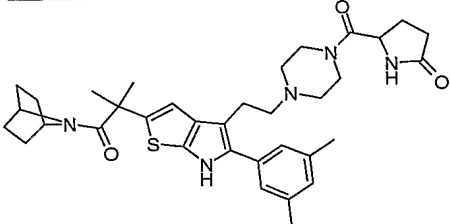
MS-ESI: 618  $[\text{M}+\text{H}]^+$

5

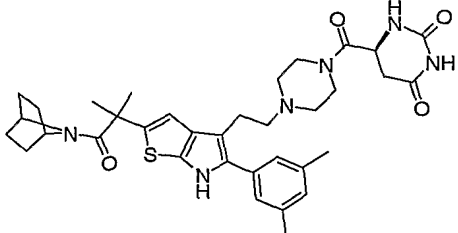
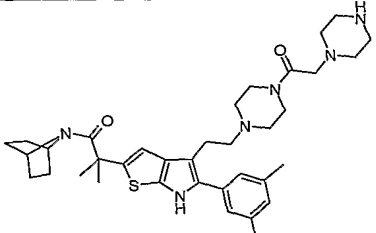
**Examples 12.1 –12.7**

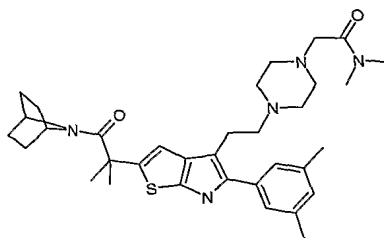
Following a procedure similar to that described in **Example 12**, the compounds of table 12 were prepared.

**Table 12**

Example		MS-ESI
12.1		616 $[\text{M}+\text{H}]^+$
12.2		626 $[\text{M}+\text{H}]^+$
12.3		618 $[\text{M}+\text{H}]^+$
12.4		627 $[\text{M}+\text{H}]^+$
12.5		616 $[\text{M}+\text{H}]^+$

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Example		MS-ESI
12.6		645 [M+H] <sup>+</sup>
12.7		631 [M+H] <sup>+</sup>

**Example 13****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-****4-[2-(4-{N,N-dimethylaminocarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-****5 dimethylphenyl)-6H-thieno[2,3-b]pyrrole**

Example 13 was prepared following a procedure similar to that described in Example 11.

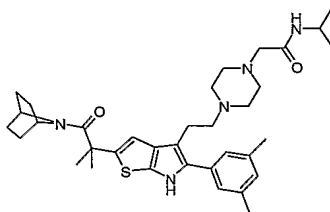
Yield: 89%

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.2-1.4 (m, 4H); 1.63 (s, 6H); 1.5-1.8 (m, 4H); 2.36 (s, 6H); 2.63 (s, 6H);  
 10 2.5-2.7 (m, 10H); 2.9-3 (m, 2H); 3.18 (s, 2H); 4-4.2 (m, br, 1H); 4.65-4.85 (m, 1H); 6.75 (s,  
 5 1H); 6.95 (s, 1H); 7.08 (s, 2H); 8.52 (s, 1H). MS-ESI: 590[M+H]<sup>+</sup>

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**Example 14**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-  
4-[2-{4-(N-isopropylaminocarbonylmethyl)piperazin-1-yl}ethyl]-5-(3,5-  
dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole**



5

Example 14 was prepared following a procedure similar to that described in Example 10.

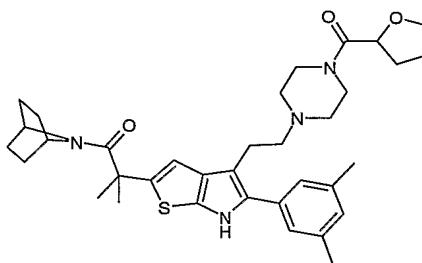
Yield: 68%

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.15 (d, 6H); 1.2-1.4 (m, 4H); 1.6 (s, 6H); 1.5-1.8 (m, 4H); 2.3 (s, 6H); 2.45-2.7 (m, 10H); 2.85-3 (m, 2H); 2.95 (s, 2H); 4-4.20 (m, br, 2H); 4.6-4.8 (m, br, 1H); 6.71  
10 (s, 1H); 6.93 (m, 2H); 7.04 (s, 2H); 8.12 (s, 1H).

MS-ESI: 604[M+H]<sup>+</sup>

**Example 15**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-  
15 4-[2-(4-{tetrahydrofuran-2-ylcarbonyl}piperazin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-  
thieno[2,3-*b*]pyrrole**



Example 15 was prepared following a procedure similar to that described in Example 10.

Yield: 73%

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.2-1.4 (m, 4H); 1.5-1.7 (m, 4H); 1.6 (s, 6H); 1.8-2.3 (m, 4H); 2.35 (s, 6H); 2.4-2.55 (m, 4H); 2.65-2.75 (m, 2H); 2.9-3 (m, 2H); 3.5-3.7 (m, 4H); 3.8-4 (m, 2H); 4-4.2 (m, br, 1H); 4.6 (m, 1H); 4.6-4.8 (m, br, 1H); 6.73 (s, 1H); 6.95 (s, 1H); 7.06 (s, 2H); 8.16  
20 (s, 1H).

MS-ESI: 603[M+H]<sup>+</sup>

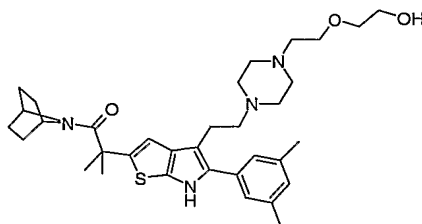
25



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**Example 16**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-(4-{hydroxyethoxyethyl}piperazin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**



5

Example 16 was prepared following a procedure similar to that described in Example 10.

Yield: 34%

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ) : 1.2-1.4 (m, 4H); 1.5-1.65 (m, 4H); 1.55 (s, 6H); 2.34 (s, 6H); 2.4-2.7 (m, 12H); 2.9 (br s, 2H); 3.48 (t, 2H); 3.56 (t, 2H); 3.58 (br s, 2H); 4.1 (br s, 1H); 4.6 (br s, 1H); 6.73 (br s, 1H); 6.9 (s, 1H); 7.08 (s, 2H); 11-12 (br s, 1H).

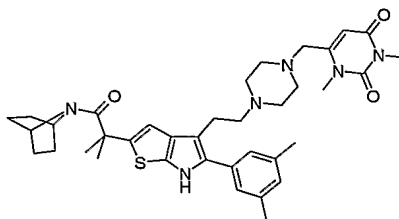
10

MS-ESI: 593[M+H]<sup>+</sup>

**Example 17**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-(4-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-ylmethyl)piperazin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**

15



Example 17 was prepared following a procedure similar to that described in Example 11.

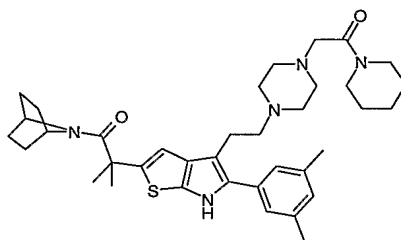
Yield: 54%

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) (  $\delta$  ppm) 1.22-1.44 (m, 4H); 1.52 – 1.79 (m, 10H); 2.34 (s, 6H); 2.44 – 2.73 (m, 8H); 2.93 (m, 2H); 3.26 (s, 2H); 3.34 (s, 3H); 3.42 (s, 3H); 4.10 (br s, 1H); 5.75 (br s, 1H); 5.73 (s, 1H); 6.73 (s, 1H); 6.94 (s, 1H); 7.03 (s, 2H); 8.12 (s, 1H).

20

MS-ESI: 657[M+H]<sup>+</sup>

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**Example 18****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-****4-[2-(4-{piperidin-1-ylcarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**

5

Example 18 was prepared following a procedure similar to that described in Example 11.

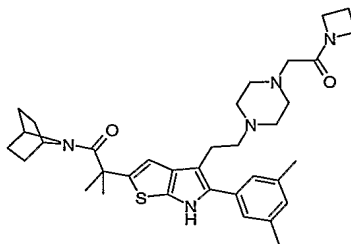
Yield: 50%

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.2-1.4 (m, 6H); 1.6 (s, 6H); 1.5-1.8 (m, 10H); 2.35 (s, 6H); 2.45-2.7 (m, 8H); 2.9-3 (m, 2H); 3.17 (s, 2H); 3.45-3.6 (m, 4H); 4.0-4.2 (m, br, 1H); 6.6-6.8 (m, br, 1H);

10 6.74 (s, 1H); 6.94 (s, 1H); 7.06 (s, 2H); 8.11 (s, 1H).

MS-ESI: 630[M+H]<sup>+</sup>**Example 19****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-**

15 **4-[2-(4-{azetidin-1-ylcarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**



Example 19 was prepared following a procedure similar to that described in Example 11.

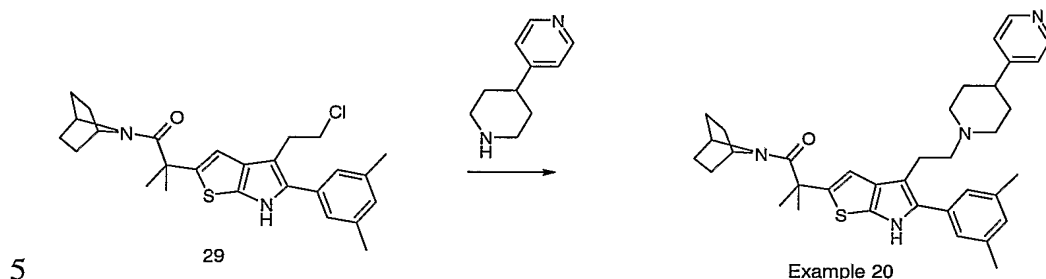
Yield: 50%

20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.2-1.4 (m, 6H); 1.45-1.8 (m, 6H); 1.6 (s, 6H); 2.25-2.35 (m, 2H); 2.35 (s, 6H); 2.45-2.7 (m, 6H); 2.9-3 (m, 2H); 3.00 (s, 2H); 4.0-4.1 (m, 2H); 4.0-4.2 (m, br, 1H); 4.2-4.3 (m, 2H); 4.6-4.8 (m, br, 1H); 6.74 (s, 1H); 6.94 (s, 1H); 7.06 (s, 2H); 8.15 (1H).

MS-ESI: 602[M+H]<sup>+</sup>

**Example 20**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-(4-pyrid-4-ylpiperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**



A mixture of **29** (0.252 g; 0.555 mmol), 4-(4-piperidinyl) pyridine (0.090 g, 0.555 mmol),  $K_2CO_3$  (0.092 g; 0.66 mmol) in acetonitrile (2 ml) was heated at 85°C under argon atmosphere for 2 hours. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 5-7% of 3.5 N  $NH_3$  in MeOH / methylene chloride to give after trituration in ether/pentane Example **20** as a solid.

Yield: 34%

$^1H$  NMR ( $CDCl_3$ ) : 1.2-1.45 (m, 4H); 1.65 (s, 6H); 1.5-1.8 (m, 4H); 1.8-1.95 (m, 4H); 2.18 (t, 2H); 2.38 (s, 6H); 2.5-2.6 (m, 1H); 2.7-2.8 (m, 2H); 2.95-3.05 (m, 2H); 3.15-3.25 (m, 2H); 4-4.2 (m, br, 1H); 4.65-4.85 (m, br, 1H); 6.78 (s, 1H); 6.98 (s, 1H); 7.10 (s, 2H); 7.18 (d, 2H); 8.22 (s, 1H); 8.53 (d, 2H).

MS-ESI: 581[M+H]<sup>+</sup>

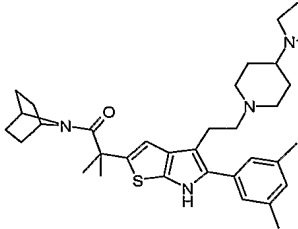
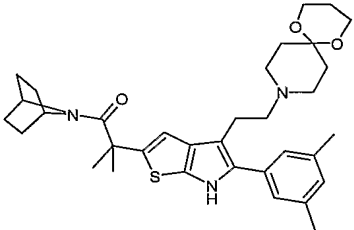
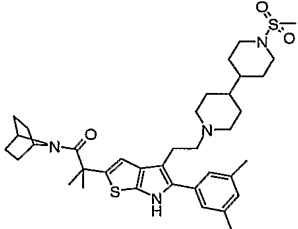
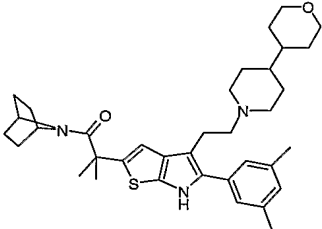
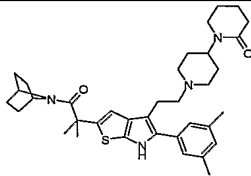
**Examples 20.1 –20.6**

Following a procedure similar to that described in Example **20**, the compounds of table **20** were prepared.

**Table 20**

Example		MS-ESI
20.1		589 [M+H] <sup>+</sup>

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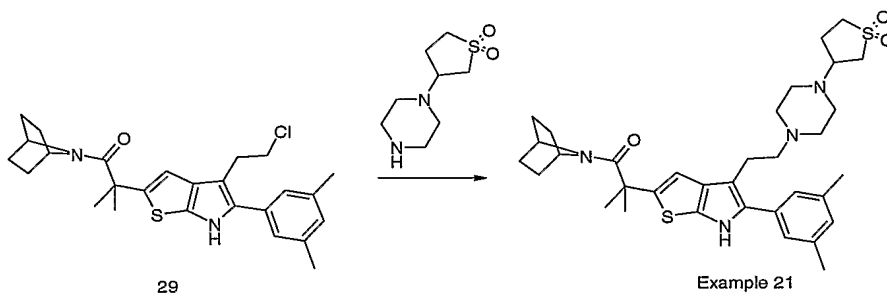
Example		MS-ESI
20.2		573 [M+H] <sup>+</sup>
20.3		576 [M+H] <sup>+</sup>
20.4		665 [M+H] <sup>+</sup>
20.5		588 [M+H] <sup>+</sup>
20.6		601 [M+H] <sup>+</sup>

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**Example 21**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-{4-(1,1-dioxidotetrahydrothien-3-yl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**

5



A mixture of **29** (0.28 g; 0.5mmol), 1-(1,1-dioxo-tetrahydro-1-gamma-(6)-thiophene-3-yl)-piperazine (0.24g; 1.mmol), DIEA (0.435ml; 2.5 mmol) and NaI (0.074 g;0.5 mmol) in DMF (4ml) was heated at 110°C under argon atmosphere for 24 hours. After extraction with ethyl acetate and evaporation, the mixture was purified by flash chromatography, eluting with  
10 methylene chloride / 3.5 N NH<sub>3</sub> in MeOH to give Example **21**.

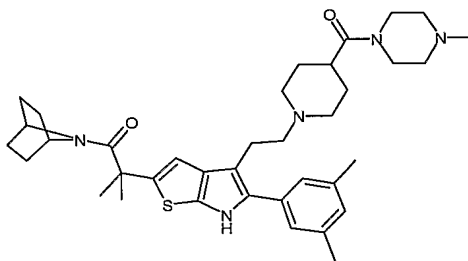
Yield: 27%

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.2-1.4 (m, 4H); 1.5-1.8 (m, 4H); 1.68 (s, 6H); 2.15 (m, 1H); 2.35 (s, 6H); 2.42 (m, 1H); 2.5-2.7 (m, 8H); 2.67 (m, 2H); 2.92 (m, 2H); 3-3.1 (m, 2H); 3.2-3.3 (m, 3H); 4.0-4.2 (m, br, 1H); 4.6-4.8 (m, br, 1H); 6.73 (s, 1H); 6.95 (s, 1H); 7.06 (s, 2H); 8.17 (s, 1H).

15 MS-ESI: 623[M+H]<sup>+</sup>**Example 22**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-{4-(4-methylpiperazin-1-ylcarbonyl)piperidin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**

20



Example 22 was prepared following a procedure similar to that described in Example **5** .

Yield: 71%

**- 133 -**

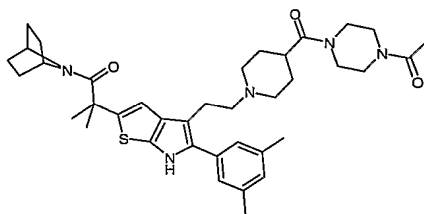
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.2-1.4 (m, 6H); 1.45-1.75 (m, 6H); 1.6 (s, 6H); 1.85-2 (m, 2H); 2.0-2.1 (m, 2H); 2.25-2.5 (m, 3H); 2.31 (s, 3H); 2.37 (s, 6H); 2.6-2.7 (m, 2H); 2.9-3.15 (m, 4H); 3.45-3.7 (m, 4H); 4.0-4.2 (m, br, 1H); 4.6-4.8 (m, br, 1H); 6.74 (s, 1H); 6.94 (s, 1H); 7.07 (s, 2H); 8.13 (s, 1H).

5 MS-ESI: 630  $[\text{M}+\text{H}]^+$

**Example 23**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-{4-(4-acetylpiperazin-1-ylcarbonyl)piperidin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-**

10 **6H-thieno[2,3-*b*]pyrrole**



Example 23 was prepared following a procedure similar to that described in Example 5.

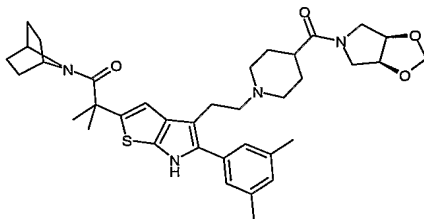
Yield: 26%

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.2-1.4 (m, 4H); 1.5-1.8 (m, 6H); 1.62 (s, 6H); 1.85-2.14 (m, 4H); 2.13 (s, 3H); 2.35 (s, 6H); 2.4-2.5 (m, 1H); 2.6-2.75 (m, 2H); 2.9-3.15 (m, 4H); 3.4-3.7 (m, 8H); 4.0-4.2 (m, 1H); 4.6-4.8 (m, 1H); 6.74 (s, 1H); 6.95 (s, 1H); 7.07 (s, 2H); 8.15 (s, 1H).

MS-ESI: 658  $[\text{M}+\text{H}]^+$

**Example 24**

20 **2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-{4-((3aR,6aS)-tetrahydro-3aH-[1,3]dioxolo[4,5-*c*]pyrrol-5-ylcarbonyl)piperidin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**



Example 24 was prepared following a procedure similar to that described in Example 5.

25 Yield : 26%

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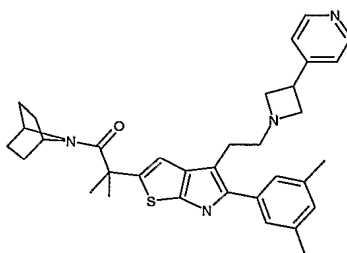
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.2-1.4 (m, 4H); 1.5-2.1 (m, 10H); 1.64 (s, 6H); 2.3-2.4 (m, 1H); 2.35 (s, 6H); 2.65-2.68 (m, 2H); 2.93-2.97 (m, 2H); 3.06-3.08 (m, 2H); 3.35-3.54 (m, 2H); 3.82-4.08 (m, 2H); 4.0-4.2 (m, br, 1H); 4.69-4.70 (m, 3H); 4.98 (d, 2H); 6.74 (s, 1H); 6.94 (s, 1H); 7.07 (s, 2H); 8.15 (s, 1H).

5 MS-ESI: 645  $[\text{M}+\text{H}]^+$

**Example 25**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-**

**4-[2-(3-pyrid-4-ylazetidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrole**



10

Example 25 was prepared following a procedure similar to that described in **Example 4**.

Yield : 26%

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.1-1.3 (m, 4H); 1.35-1.7 (m, 4H); 1.52 (s, 6H); 2.24 (s, 6H); 2.74-2.8 (m, 4H); 3.05-3.2 (m, 2H); 3.5-3.7 (m, 3H); 3.95-4.15 (m, 1H); 4.5-4.7 (m, 1H); 6.67 (s, 1H); 6.84 (s, 1H); 7.01 (s, 2H); 7.09 (d, 2H); 8.42 (d, 2H); 8.75 (s, 1H).

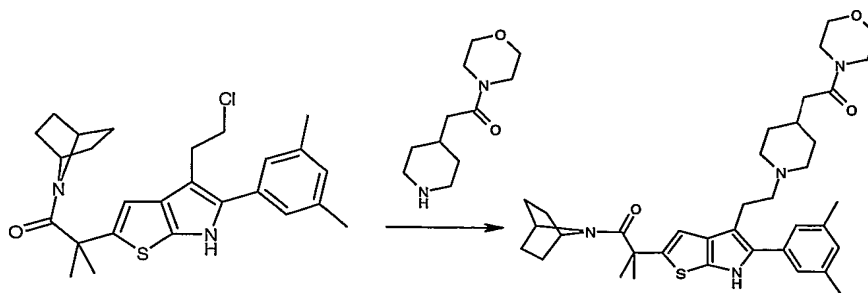
15

MS-ESI:  $[\text{M}+\text{H}]^+$

**Example 26**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-**

**4-[2-(4-{morpholinocarbonylmethyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrole**



29

Example 26

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A mixture of **29** (0.137 g; 0.3 mmol), 4-(4-piperidinylacetyl) morpholine (0.127 g, 0.51 mmol), K<sub>2</sub>CO<sub>3</sub> (0.112 g; 0.81 mmol) in DMA (3 ml) was heated at 85°C under argon atmosphere for 6 hours. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 5-7% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give after trituration in ether/pentane Example **26** as a solid.

Yield: 71%

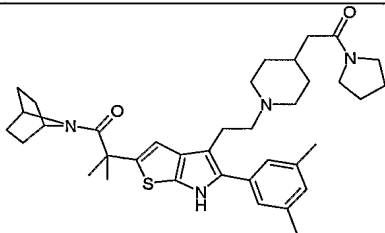
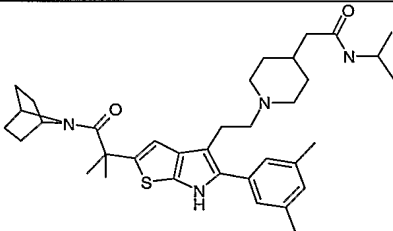
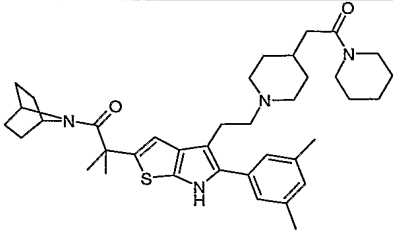
<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.2-1.4 (m, 8H); 1.6 (s, 6H); 1.5-1.8 (m, 4H); 1.75-1.85 (m, 2H); 1.8-1.95 (m, br, 1H); 2-2.15 (m, 2H); 2.25-2.26 (m, 2H); 2.35 (s, 6H); 2.6-2.7 (m, 2H); 2.9-3.1 (m, 4H); 4.45-4.55 (m, 2H); 3.6-3.7 (m, 4H); 4-4.2 (m, br, 1H); 4.65-4.85 (m, br, 1H); 6.74 (s, 1H); 6.94 (s, 1H); 7.06 (s, 2H); 8.12 (s, 1H).

MS-ESI: 631[M+H]<sup>+</sup>

### Examples 26.1 –26.5

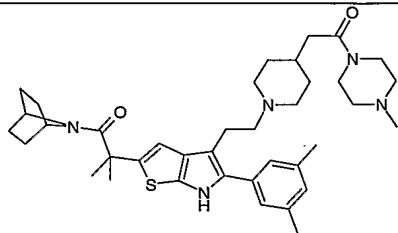
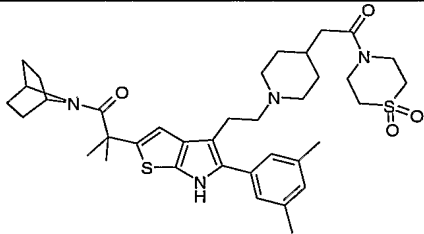
Following a procedure similar to that described in Example 26, the compounds of table 26  
15 were prepared.

### Table 26

Example		MS-ESI
26.1		615 [M+H] <sup>+</sup>
26.2		603 [M+H] <sup>+</sup>
26.3		629 [M+H] <sup>+</sup>

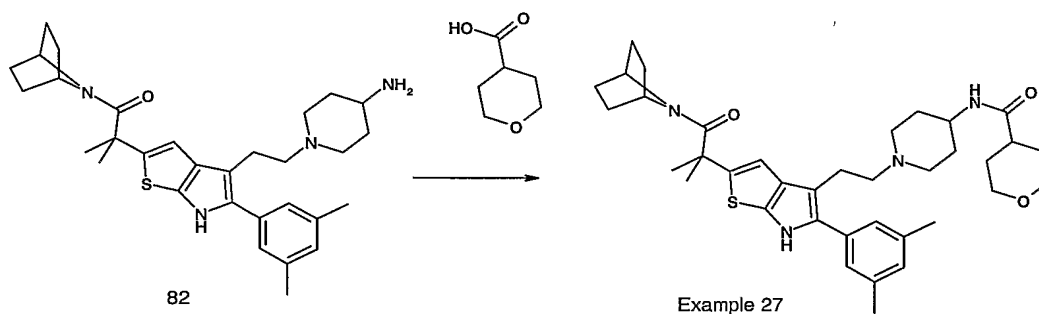


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Example		MS-ESI
26.4		644 [M+H] <sup>+</sup>
26.5		679 [M+H] <sup>+</sup>

**Example 27**

2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-(4-{tetrahydro-2H-pyran-4-ylcarbonylamino}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrole



EDC (0.091g; 0.475 mmol) was added to a stirred solution of **82** (0.176g; 0.317 mmol), HOBT (0.064g; 0.475 mmol) and tetrahydropyran-4-yl-carboxylic acid (0.11g; 0.634mmol) in DMF (3 ml). After stirring for 1 hour, the mixture was evaporated and purified by flash chromatography, eluting with MeOH / methylene chloride 3/97 to give example **27** as a solid.

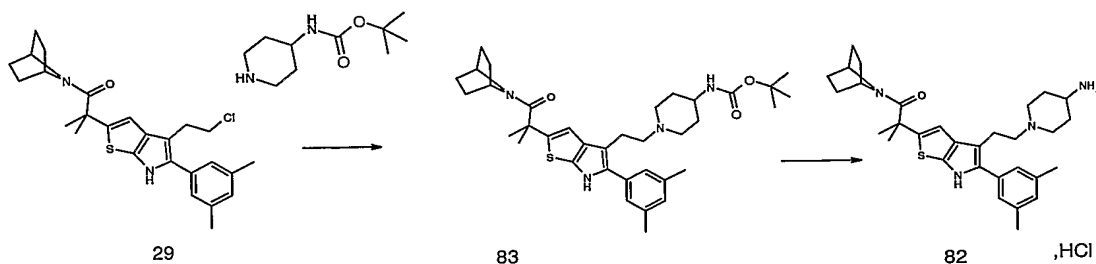
Yield: 50%

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.2-1.4 (m, 4H); 1.5-1.85 (m, 6H); 1.62 (s, 6H); 1.9-2 (m, 2H); 2.1-2.4 (m, 7H); 2.35 (s, 6H); 2.65-2.75 (m, 2H); 2.9-3.05 (m, 4H); 3.35-3.45 (m, 2H); 3.75-3.9 (m, 1H); 4.0-4.1 (m, 2H); 4.0-4.2 (m, br, 1H); 4.65-4.85 (m, br, 1H); 5.5 (d, 1H); 6.78 (s, 1H); 6.95 (s, 1H); 7.05 (s, 2H); 8.14 (s, 1H).

MS-ESI: 631[M+H]<sup>+</sup>

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The starting material was prepared as follows:



A mixture of **29** (0.1.7 g; .3.7 mmol), 4-N-(tert-butoxycarbonyl)-aminopiperidine (0.972 g, 5 4.85 mmol), NaI (0.554g; 4.85 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.67 g; 4.85 mmol) in dimethylacetamide (17 ml) was heated at 85°C under argon atmosphere for 3 hours. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 2-4% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give after trituration in pentane **83** as a solid.

Yield: 87%

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.2-1.4 (m, 4H); 1.44 (s, 9H); 1.5-1.8 (m, 4H); 1.63 (s, 6H); 1.9-2.1 (m, 2H); 2.10-2.40 (m, 2H); 2.36 (s, 6H); 2.6-2.9 (m, 2H); 2.9-3.2 (m, 2H); 3.48-3.62 (m, 1H); 4.0-4.2 (m, 1H); 4.5 (br s, 1H); 4.6-4.85 (br s, 1H); 6.81 (br s, 1H); 6.95 (s, 1H); 7.05 (s, 2H); 8.25 (br s, 1H).

15 A solution of **83** (2g; 0.32 mmol) in dioxan (20 ml) was treated at 0°C with 12N HCl (5ml). After 1 hour, the mixture was stirred at ambient temperature for 3 hours; evaporated and trituated in ether/ pentane to give **82** as a solid.

Yield : 100%

20 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>): 1.2-1.4 (m, 4H); 1.4-1.7 (m, 4H); 1.54 (s, 6H); 2.0 (m, 2H); 2.15 (m, 2H); 2.36 (s, 6H); 3.05-3.35 (m, 6H); 3.60-3.75 (m, 2H); 4.0-4.2 (m, 1H); 4.3-4.5 (m, 1H); 6.97 (s, 1H); 6.99 (s, 1H); 7.11 (s, 2H); 8.33 (br s, 2H); 10.8 (br s, 1H); 11.49 (s, 1H).

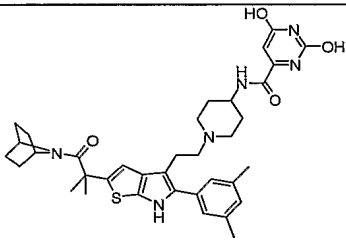
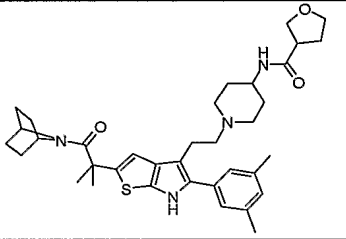
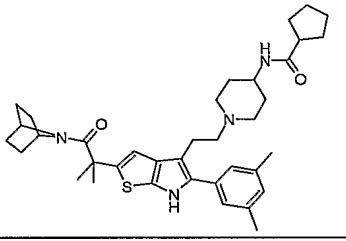
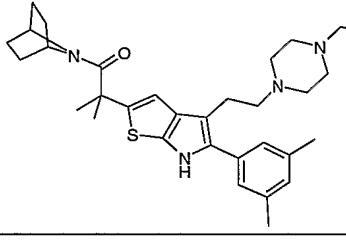
MS-ESI: 519[M+H]<sup>+</sup>

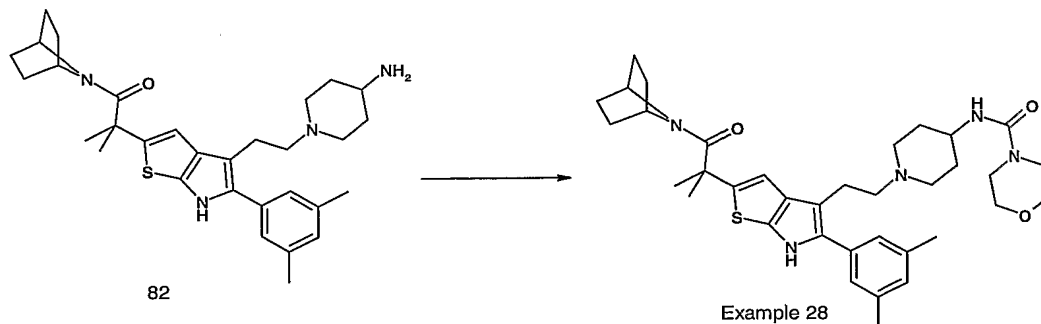
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**Examples 27.1 –27.4**

Following a procedure similar to that described in Example 27, the compounds of table 27 were prepared.

**Table 27**

Example		MS-ESI
27.1		657 [M+H] <sup>+</sup>
27.2		617 [M+H] <sup>+</sup>
27.3		615 [M+H] <sup>+</sup>
27.4		631 [M+H] <sup>+</sup>

**Example 28****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-****4-[2-(4-{morpholinocarbonylamino}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**

5

4-nitrophenylchloroformate (0.111g; 1.1mmol) was added under argon atmosphere, at 0°C to a solution of **82** (0.277g; 0.5 mmol) and triethylamine; after stirring at ambient temperature for 1 hour, morpholine (0.052ml; 0.6 mmol) was added. After 2 hours, the mixture was purified by flash chromatography eluting with a 2-8% gradient of 3.5N NH<sub>3</sub> in MeOH

10 CH<sub>2</sub>Cl<sub>2</sub> / to give after trituration with pentane-ether example **28** as a solid.

Yield : 38%

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.2-1.8 (m, 10H); 1.61 (s, 6H); 1.95-2.05 (m, 2H); 2.1-2.25 (m, 2H); 2.34 (s, 6H); 2.6-2.7 (m, 2H); 2.9-3 (m, 4H); 3.3-3.4 (m, 4H); 3.65-3.8 (m, 5H); 4.0-4.2 (m, br, 1H); 4.4 (d, 1H); 4.6-4.8 (m, br, 1H); 6.8 (s, 1H); 6.94 (s, 1H); 7.05 (s, 2H); 8.17 (s, 1H).

15 MS-ESI: 632 [M+H]<sup>+</sup>**Examples 28.1 –28.3**

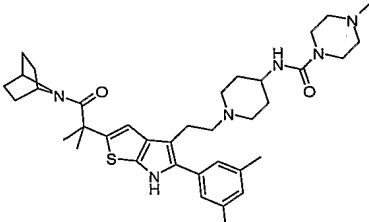
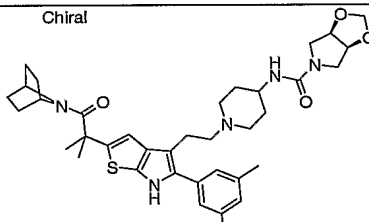
Following a procedure similar to that described in Example **28**, the compounds of table **28** were prepared.

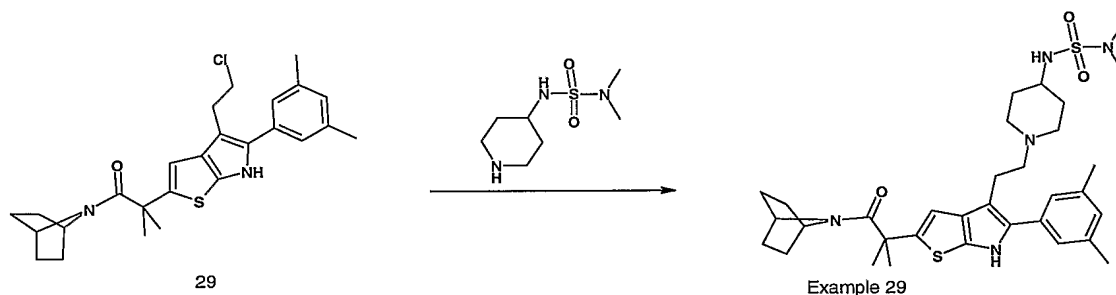
20

**Table 28**

Example		MS-ESI
28.1		630 [M+H] <sup>+</sup>

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Example		MS-ESI
28.2		645 [M+H] <sup>+</sup>
28.3	Chiral 	660 [M+H] <sup>+</sup>

**Example 29****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-****4-[2-(4-{N,N-dimethylaminosulfonylaminomethyl}piperidin-1-yl)ethyl]-5-(3,5-****5 dimethylphenyl)-6H-thieno[2,3-b]pyrrole**

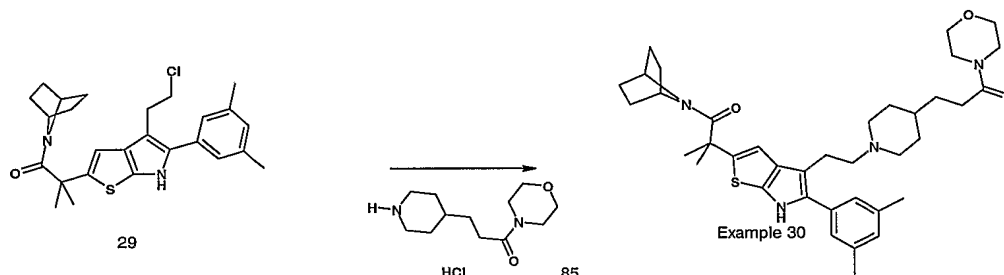
A mixture of **29** (0.225 g; 0.5 mmol), N,N-dimethyl-N'-4-piperidinyl sulfamide (0.250 g, 0.6 mmol), and K<sub>2</sub>CO<sub>3</sub> (0.083 g; 0.6 mmol) in dimethylacetamide (3 ml) was heated at 85°C under argon atmosphere for 5 hours. The crude mixture was evaporated and purified by flash chromatography eluting with 3.5 N MeOH-NH<sub>3</sub> / methylene chloride 95/5 to give after trituration in pentane Example **29** as a solid.

Yield: 50 %

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.2-1.45 (m, 4H); 1.5-1.8 (m, 6H); 1.61 (s, 6H); 2.0-2.1 (m, 2H); 2.1-2.2 (m, 2H); 2.34 (s, 6H); 2.6-2.7 (m, 2H); 2.8 (s, 6H); 2.85-2.95 (m, 4H); 3.2-3.3 (m, 1H); 4.0-4.2 (m, br, 1H); 4.28 (d, 1H); 4.6-4.8 (m, br, 1H); 6.75 (s, 1H); 6.93 (s, 1H); 7.05 (s, 2H); 8.6 (s, 1H).

MS-ESI: 626 [M+H]<sup>+</sup>

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**Example 30****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-****4-[2-(4-{3-oxo-3-morpholinoprop-1-yl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**

5

A mixture of **29** (0.137 g; 0.3 mmol), **85** (0.158 g, 0.6 mmol), K<sub>2</sub>CO<sub>3</sub> (1.24 g; 0.9 mmol) in acetonitrile (3 ml) and DMA (2ml) was heated at 85°C overnight under argon atmosphere. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 5-7% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give after trituration in ether/pentane Example **30** as a solid.

10

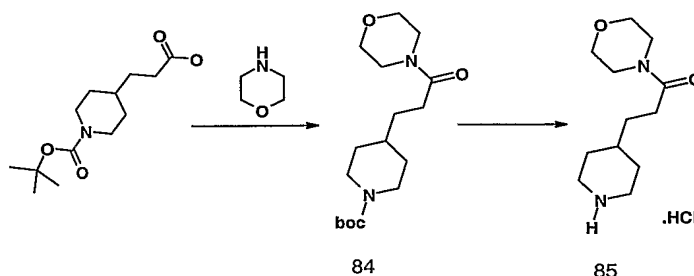
Yield: 61%

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.2-1.4 (m, 6H); 1.5-1.8 (m, 9H); 1.6 (s, 6H); 1.95-2.05 (m, br, 2H); 2.3-2.4 (m, 2H); 2.35 (s, 6H); 2.6-2.7 (m, 2H); 2.9-3.1 (m, 4H); 3.4-3.5 (m, 2H); 3.6-3.7 (m, 6H); 4.0-4.2 (m, br, 1H); 4.65-4.85 (m, br, 1H); 6.74 (s, 1H); 6.94 (s, 1H); 7.06 (s, 2H); 8.14 (s,

15

MS-ESI: 646[M+H]<sup>+</sup>

The starting material was prepared as follows:



EDC (1.25g; 6.5 mmol) was added to a stirred solution of 1-tert-butoxycarbonyl-4-piperidine propionic acid (1.29g; 5 mmol), HOBt (0.878g; 6.5 mmol) and morpholine ( 0.57g; 6.5 mmol) in methylene chloride (15 ml). After stirring for 18 hours, the mixture was evaporated and purified by flash chromatography, eluting with MeOH / methylene chloride 3/97 to give **84** as a solid.

20

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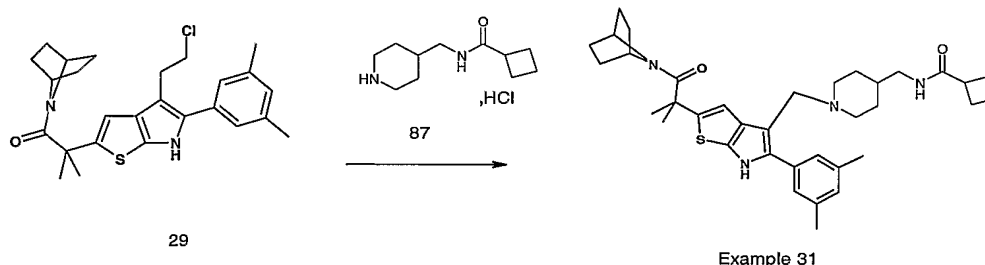
Yield: 100%

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.1-1.3 (m, 2H); 1.45 (s, 9H); 1.4-1.5 (m, 1H); 1.55-1.75 (m, 4H); 2.33 (t, 2H); 2.6-2.75 (m, 2H); 3.45 (m, 2H); 3.61 (m, 2H); 3.67 (m, 4H); 4.0-4.2 (m, 1H).

5 **84** (1.54 g; 2.45 mmol) in solution in dioxan (15ml) was treated with 12N HCl (4ml) at  $0^\circ\text{C}$ ; After stirring at ambient temperature for 2 hours, the mixture was evaporated and triturated in ether to give **85** as a solid.

Yield: 100%

$^1\text{H}$  NMR (DMSO): 1.28-1.34 (m, 2H); 1.42-1.45 (m, 3H); 1.79 (d, 2H); 2.32 (t, 2H); 2.7-2.85  
10 (m, 2H); 3.20 (d, 2H); 3.41 (m, 4H); 4.5-4.6 (m, 4H); 8.71 (m, br, NH).

**Example 31****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-****4-[4-(cyclobutylcarbonylaminomethyl)piperidin-1-ylmethyl]-5-(3,5-dimethylphenyl)-**15 **6H-thieno[2,3-b]pyrrole**

A mixture of **29** (0.115 g; 0.25 mmol), **87** (0.116 g, 0.5 mmol),  $\text{K}_2\text{CO}_3$  (0.07 g; 0.5 mmol) in acetonitrile (2 ml) and DMF (0.5 ml) was heated at  $85^\circ\text{C}$  for 3 hours under argon atmosphere  
20 . The crude mixture was purified by flash chromatography eluting successively with AcOEt / methylene chloride 50/50, AcOEt and 3.5 N  $\text{NH}_3$  in MeOH / AcOEt 10 /90 to give after trituration in ether/pentane Example **31** as a solid.

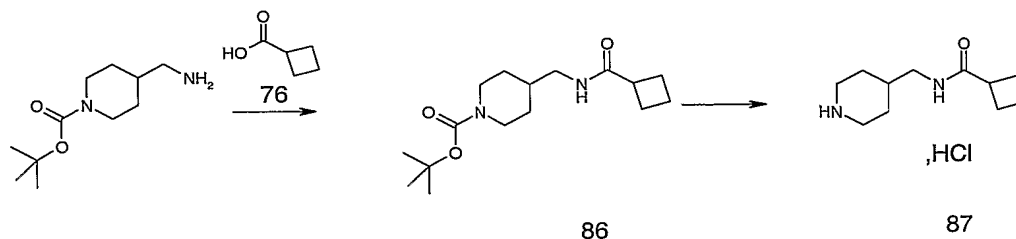
Yield: 90 %

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) ( $\delta$  ppm) 1.26 – 1.32 (m, 6H); 1.45 – 1.75 (m, 8H); 1.61 (s, 6H); 1.8  
25 2.3 (m, 8H); 2.34 (s, 6H); 2.6 – 2.75 (br s, 2H); 2.9 – 3.15 (m, 6H); 4.1 (br s, 1H); 4.75 (br s, 1H); 5.45 (br s, 1H); 6.72 (s, 1H); 6.944 (s, 1H); 7.058 (s, 2H); 8.19 (1H).

MS-ESI: 615  $[\text{M}+\text{H}]^+$

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The starting material was prepared as follows:



1-tert-butoxycarbonyl-4-aminomethyl piperidine (0.645 mg; 3 mmol) was added, under argon atmosphere to a stirred solution of cyclobutane carboxylic acid (0.3g; 3 mmol), EDC (0.864g; 4 mmol), DIEA (0.78ml; 4.5 mmol) and DMAP (0.055g; 0.45 mmol) in methylene chloride (30 ml). The mixture was stirred overnight, evaporated and purified by flash chromatography, eluting successively with methylene chloride, AcOEt and 3.5 N NH<sub>3</sub> in MeOH / AcOEt 10 /90 to give 1 as a solid.

Yield : 56%

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.23 (m, 2H); 1.44 (s, 9H); 1.61–1.65 (m, 3H); 1.80–2.30 (ms, 6H); 2.68 (br 2H); 2.98 (m, 1H); 3.12 (br s, 2H); 4.12 (br s, 2H); 5.42 (br s, 1H).

**86** (0.44g; 1.35 mmol) was dissolved in dioxan (3 ml) and treated with a solution made of 12N HCl / dioxan 5/25 (3 ml). The mixture was heated at 55°C under argon atmosphere overnight. After evaporation to dryness, the residue was triturated in a mixture of MeOH, methylene chloride and ether to give **87** as solid.

Yield: 69%

<sup>1</sup>H NMR ( DMSO-d<sub>6</sub> ) 1.25 (m , 2H); 1.60–1.80 (m, 4H); 1.87 ( m ,1H); 1.99 (m, 2H ); 2.08 ( 2H); 2.77 (m, 2H) ; 2.80 – 3.05 (m, 3H); 3.37 (m, 2H).

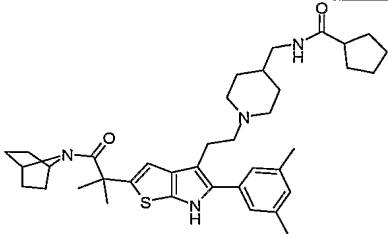
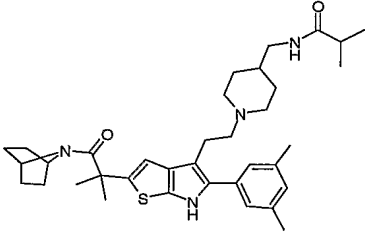
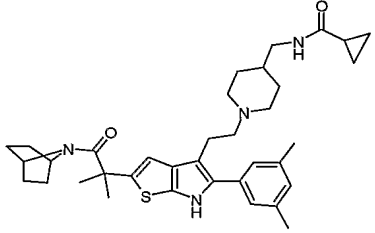
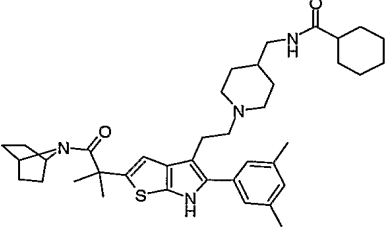


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**Examples 31.1-31.4**

Following a procedure similar to that described in Example 31 the compounds of table 31 were prepared.

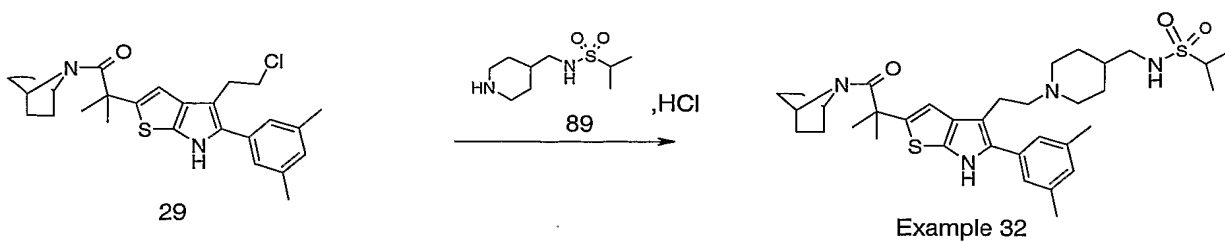
**Table 31**

Example		MS-ESI
31.1		629 [M+H] <sup>+</sup>
31.2		603 [M+H] <sup>+</sup>
31.3		601 [M+H] <sup>+</sup>
31.4		643 [M+H] <sup>+</sup>

5

**Example 32**

2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-  
4-[2-(4-{isopropylsulphonylaminomethyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-  
6H-thieno[2,3-b]pyrrole



10

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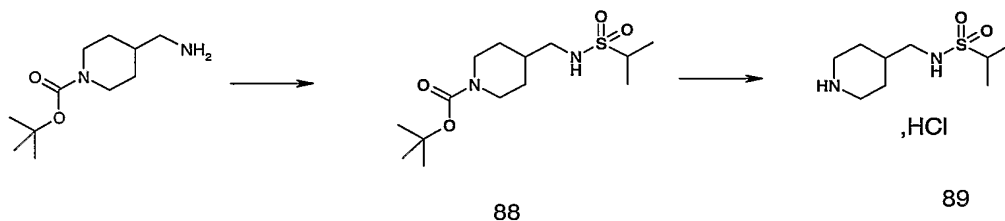
Example **32** was prepared following a method described in Example **31**.

Yield: 88%

$^1\text{H}$  NMR(  $\text{CDCl}_3$  ): 1.25–1.40 (m, 4H); 1.38 (d, 6H); 1.45 –1.80 (m, 7H); 1.62 (s, 6H); 1.90–2.10 (br s, 2H); 2.35 (s, 6H); 2.6–2.80 (br s, 2H); 2.90–3.15 (m, 8H); 3.15 (s, 1H); 4.10 (br s, 2H); 4.75 (br s, 1H); 6.75 (s, 1H); 6.95 (s, 1H); 7.05 (s, 2H); 8.16 (s, 1H).

MS-ESI: 639[M+H]<sup>+</sup>

The starting material was prepared as follows:



10 Isopropylsulfonyl chloride (0.230 ml; 2.05 mmol) was added under argon atmosphere at 0°C to solution of 1-*t*-butoxycarbonyl-4-aminomethyl-piperidine (0.4g; 1.87 mmol) and  $\text{K}_2\text{CO}_3$  (0.285 g; 2.05 mmol) in acetonitrile (15 ml). The mixture was stirred overnight at ambient temperature and purified by flash chromatography eluting successively with methylene chloride, AcOEt / methylene chloride 80/20 to give **88** as a solid.

15 Yield : 41%

$^1\text{H}$  NMR (  $\text{CDCl}_3$  ) 1.13 (m, 2H); 1.38 (d, 6H); 1.45 (s, 9H); 1.60–1.80 (m, 3H); 2.68 (br s, 2H); 3.04 (m, 2H); 3.16 (m, 1H); 4.06 – 4.20 (br s, 3H).

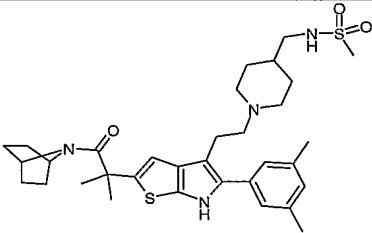
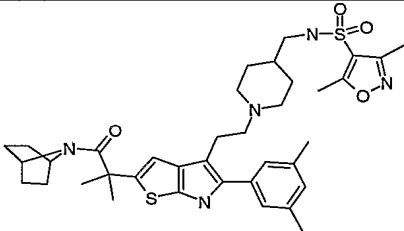
**88** (0.340g; 0.94 mmol) was dissolved in dioxan (3 ml) / methylene chloride (0.3 ml) and treated with a solution made of 12N HCl / dioxan 5/25 (2 ml). The mixture was stirred at ambient temperature under argon atmosphere overnight. After evaporation to dryness, the residue was triturated in a mixture of MeOH, methylene chloride and ether to give **89** as solid.

Yield: 100%

25  $^1\text{H}$  NMR (  $\text{CDCl}_3$  ) 1.35 (d, 6H); 1.66 (m, 2H); 1.81 (br s, 1H); 1.92 (m, 2H); 3.08 (m, 2H); 3.15 (m, 1H); 3.51 (m, 2H).

### Examples 32.1 –32.2

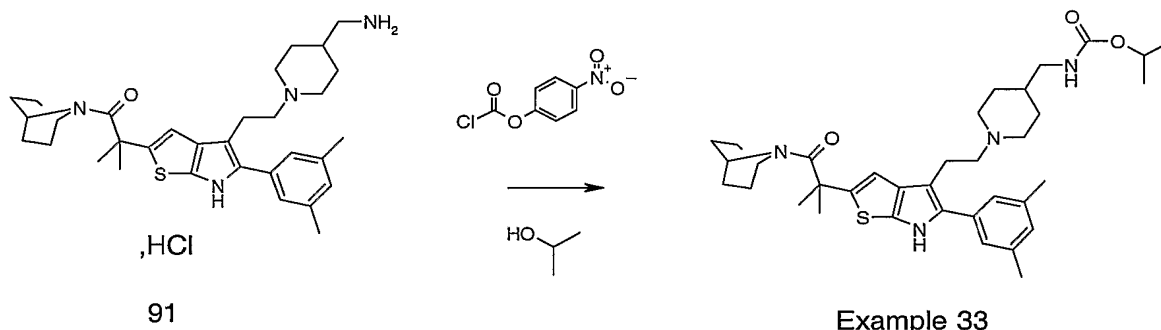
Following a procedure similar to that described in Example 32, the compounds of table 32 were prepared.

Example		MS-ESI
32.1		611 [M+H] <sup>+</sup>
32.2		692 [M+H] <sup>+</sup>

### 5 Example 33

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-**

**4-[2-(4-{isopropoxycarbonylaminomethyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole**



10 4-nitrophenylchloroformate (0.110. g; 0.55 mmol) was added under argon atmosphere, at 0°C to a solution of **91** (0.284 g; 0.5 mmol) and triethylamine (0.135 ml; 1.05mmol) in methylene chloride (12 ml); after stirring at ambient temperature for 1 hour and evaporation , isopropanol (10 ml) was added. The mixture was refluxed for 7 hours, evaporate to dryness and purified on reverse phase chromatography eluting with a 10-80% gradient of MeOH /  
15 (NH<sub>4</sub>)<sub>2</sub>CO<sub>3</sub> – H<sub>2</sub>O 2g/l to give after trituration with pentane-ether example **33** as a solid.  
Yield : 52%

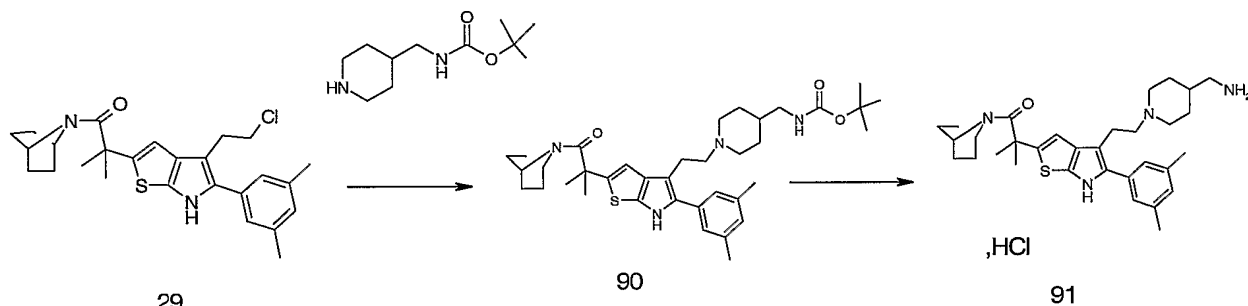
**- 147 -**

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.22 (d, 6H); 1.20-1.35 (m, 6H); 1.45-1.85 (m, 7H); 1.60 (s, 6H); 2.01 (br s, 2H); 2.35 (s, 6H); 2.66 (br s, 2H); 2.90-3.12 (m, 6H); 4.10 (br s, 1H); 4.67 (m, 2H); 4.89 (m, 1H); 6.74 (s, 1H); 6.94 (s, 1H); 7.06 (s, 2H); 8.13 (s, 1H).

MS-ESI: 619[M+H] $^+$

5

The starting material was prepared as follows:



A mixture of **29** (3.27 g; 7.2 mmol), 4-tert-butoxycarbonylaminomethyl piperidine (03.08 g, 14.2 mmol),  $\text{K}_2\text{CO}_3$  (1.95 g; 14.2 mmol) in acetonitrile (50 ml) and DMF (0.5 ml) was heated at 85°C for 3 hours under argon atmosphere. The crude mixture was purified by flash chromatography eluting successively with AcOEt / methylene chloride 50/50, AcOEt and 3.5 N  $\text{NH}_3$  in MeOH / AcOEt 20 / 80 to give **90** as a solid.

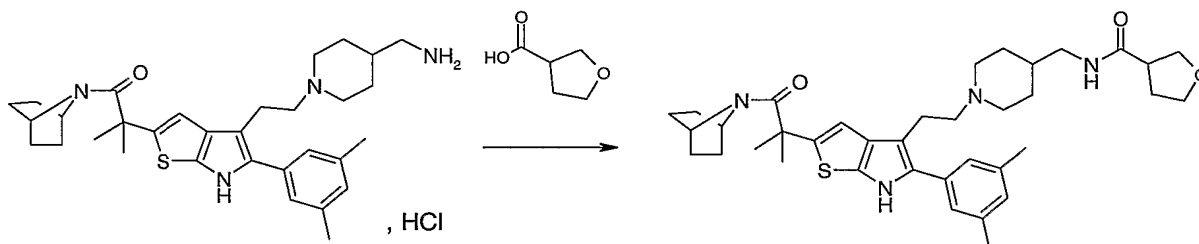
Yield: 80 %

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 1.26–1.40 (m, 6H); 1.44 (s, 9H); 1.45–1.75 (m, 7H); 1.59 (s, 6H); 2.00 (br s, 2H); 2.35 (s, 6H); 2.66 (m, 2H); 2.93–3.49 (ms, 6H); 4.10 (br s, 1H); 4.61 (br s, 1H); 4.7 (br s, 1H); 6.74 (s, 1H); 6.94 (s, 1H); 7.06 (s, 2H); 8.13 (s, 1H).

**90** (3.06g; 4.84 mmol) was dissolved in dioxan (13 ml) and treated with a solution made of 12N HCl / dioxan 5/25 (9.7 ml). The mixture was stirred at ambient temperature under argon atmosphere overnight. After evaporation to dryness, the residue was triturated in a mixture of MeOH, methylene chloride and ether to give **91** as solid.

Yield: 100%

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ ) 1.26 – 1.45 (m, 6H); 1.40–1.70 (m, 7H); 1.52 (s, 6H); 1.80–2.00 (m, 3H); 2.00 (m, 2H); 2.34 (s, 6H); 2.66 (m, 2H); 3.60 (m, 2H); 4.1 (br s, 1H); 4.55 (br s, 1H); 4.75 (br s, 1H); 6.95 (s, 1H); 6.98 (s, 1H); 7.10 (s, 2H); 8.07 (s, 1H).

**Example 34****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-****4-[2-(4-{tetrahydrofuran-2-ylcarbonylaminomethyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrole**

91

Example 34

To a suspension of tetrahydro-3-furoic acid (0.029 g; 0.25 mmol) in methylene chloride ( 2m was added DIEA (0.190 ml; 1.09 mmol), HATU (0.104g; 0.275 mmol) and **91** (0.146 g; 0. mmol). The mixture was stirred at ambient temperature overnight. The crude mixture was purifi

10 NH<sub>3</sub> in MeOH/AcOEt 5 / 95 to give **Example 34** as a solid.

Yield: 83%

<sup>1</sup>H NMR ( CDCl<sub>3</sub> ) : 1.20–1.45 (m, 6H); 1.45–1.85 (m, 7H); 1.61 (s, 6H); 2.00 (m, 2H); 2. (m, 2H); 2.34 (s, 6H); 2.64 (m, 2H); 2.90 (m, 3H); 3.01 (m, 2H); 3.16 (t, 2H); 3.80 (m, 1H); 3. (m, 2H); 3.94 (m, 1H); 4.10 (br s, 2H); 4.75 (br s, 1H); 6.74 (s, 1H); 6.94 (s, 1H); 7.05 (s, 2H)

15 8.15 (s, 1H).

MS-ESI: 631[M+H]<sup>+</sup>**Examples 34.1–34.6**

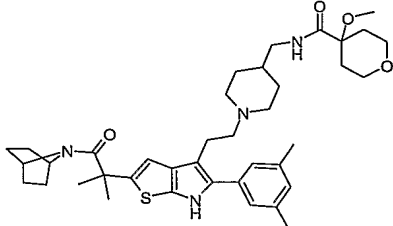
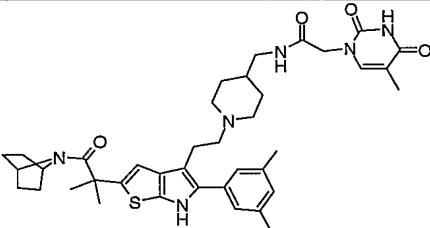
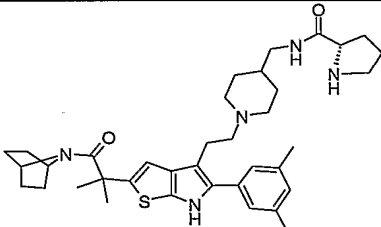
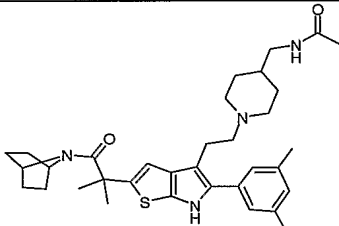
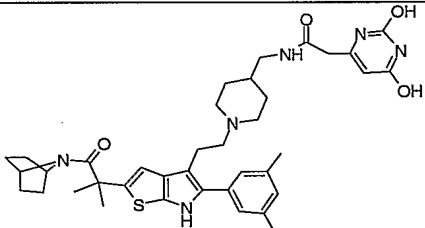
Following a procedure similar to that described in Example **34**, the compounds of table **34**

20 were prepared.

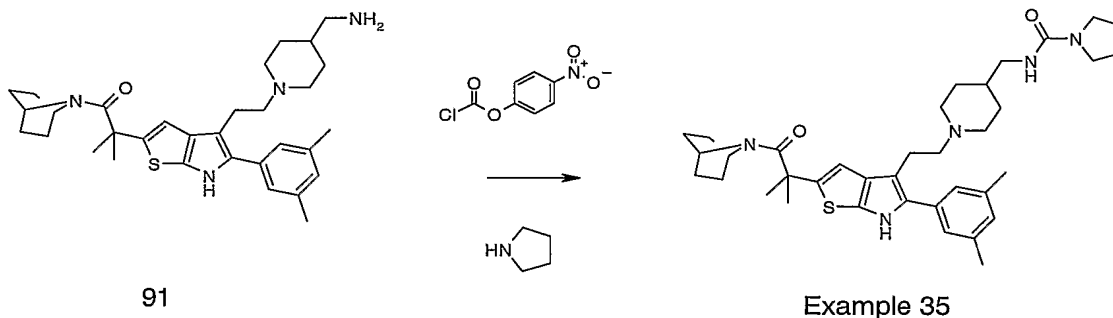
**Table 34**

Example		MS-ESI
34.1		671 [M+H] <sup>+</sup>

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Example		MS-ESI
34.2		675 [M+H] <sup>+</sup>
34.3		699 [M+H] <sup>+</sup>
34.4		630 [M+H] <sup>+</sup>
34.5		575 [M+H] <sup>+</sup>
34.6		685 [M+H] <sup>+</sup>

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**Example 35****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-****4-[2-(4-{pyrrolidin-1-ylcarbonylmethyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**

5

4-nitrophenylchloroformate (0.056. g; 0.275 mmol) was added under argon atmosphere , at 0°C to a solution of **91** (0.250 g; 0.25 mmol) and triethylamine (0.074 ml; 0.525 mmol) in methylene chloride (3 ml); after stirring at ambient temperature for 1 hour, pyrrolidine (0.023 ml) was added. The mixture was stirred at ambient temperature overnight, evaporated to dryness and purified by flash chromatography eluting with 3.5 N NH<sub>3</sub> in MeOH / methylene chloride 6/ 94 to give example **35** as a solid.

Yield : 78%

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.20–1.35 (m, 4H); 1.45–1.75 (m, 4H); 1.64 (s, 6H); 1.45–1.95 (m, 10H); 2.03 (m, 2H); 2.36 (s, 6H); 2.60 (m, 2H); 3.12 (m, 2H); 3.18 (m, 6H); 3.54 (m, 2H); 4.18 (br s, 1H); 4.70 (br s, 1H); 6.90 (s, 1H); 6.93 (s, 1H); 7.03 (s, 2H); 8.55 (s, 1H).

15

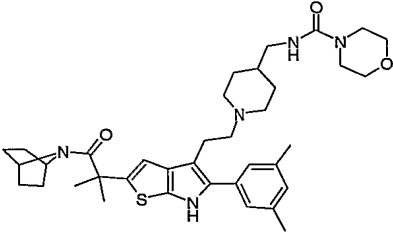
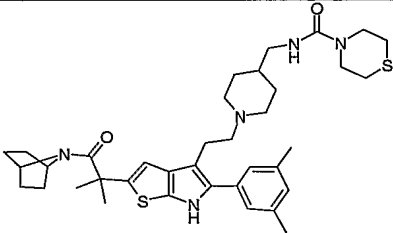
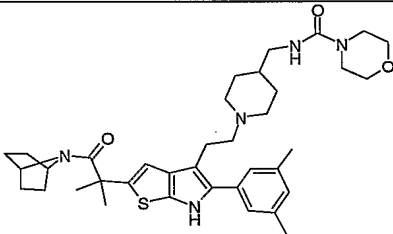
**Examples 35.1–35.4**

Following a procedure similar to that described in Example **35**, the compounds of table **35** were prepared.

20

Example		MS-ESI
35.1		618 [M+H] <sup>+</sup>

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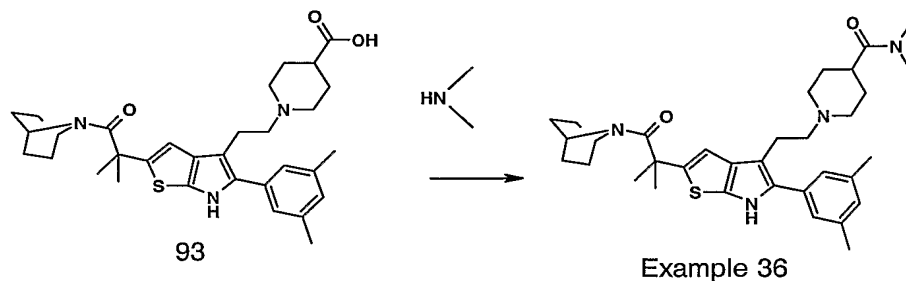
Example		MS-ESI
35.2		646 [M+H] <sup>+</sup>
35.3		662 [M+H] <sup>+</sup>
35.4		646 [M+H] <sup>+</sup>

**Example 36**

2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-

4-[2-(4-{N,N-dimethylaminocarbonyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-

5 6H-thieno[2,3-b]pyrrole



A mixture of **93** (0.137g, 0.25 mmol), HATU (0.152g; 0.4mmol) and DIEA (0.09 ml; 0.5 mmol) in DMF (2ml) was stirred at ambient temperature for 2 hours. The crude material was purified on reverse phase silica eluting with a gradient of 10-80% acetonitrile / 1% acetic acid-H<sub>2</sub>O. The appropriate fractions were evaporated and triturated in ether to give Example 34 as a solid.

Yield : 54%



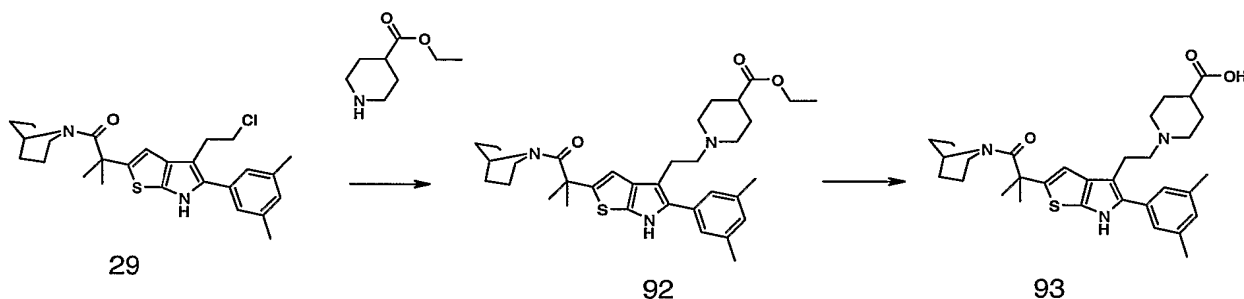
## - 152 -

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ ) : 1.25-1.75 (m, 8H); 1.61 (s, 6H); 1.9-2.1 (m, 4H); 2.37 (6H); 2.9-3.24 (m, 13H); 3.45-3.5 (m, 2H); 4.0-4.2 (br m, 1H); 4.6-4.8 (m, 1H); 6.77 (s, 1H); 6.98 (s, 1H); 7.05 (m, 2H).

MS-ESI: 575  $[\text{M}+\text{H}]^+$

5

The starting material was prepared as follows:



A mixture of **29** (4.55g; 0.01 mol), 4-ethoxycarbonyl piperidine (2.36g; 0.015 mol), triethylamine (1.53ml; 0.011mol) and NaI (1.5g; 0.01mol) in DMA (45ml) was heated at 110°C under argon atmosphere for 4 hours. After extraction with ethyl acetate and evaporation, the mixture was purified by flash chromatography, eluting with a gradient 80-100% ethyl acetate / petroleum ether to give **92**.

Yield: 62%

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 1.25 (t, 3H); 1.2-1.45 (m, 4H); 1.5-1.8 (m, 4H); 1.62 (s, 6H); 1.7-2 (m, 4H); 2.05-2.15 (m, 2H); 2.25-2.35 (m, 1H); 2.35 (s, 6H); 2.64-2.67 (m, 2H); 2.93-2.98 (m, 4H); 4.13 (q, 2H); 4.0-4.2 (br m, 1H); 4.6-4.8 (br m, 1H); 6.74 (s, 1H); 6.94 (s, 1H); 7.07 (s, 2H); 8.13 (s, 1H).

A solution of **92** (3.61g; 0.627 mmol) in 2N NaOH (5ml) and EtOH (100ml) was heated at 60°C for 2 hours. After extraction with methylene chloride / methanol (50/50) and evaporation, the residue was triturated in ether to give **93** as a solid.

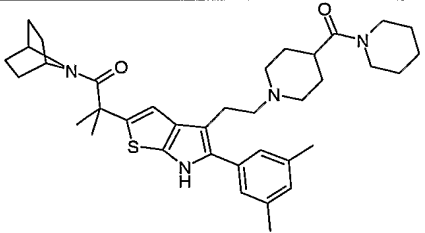
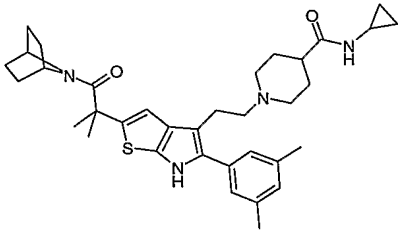
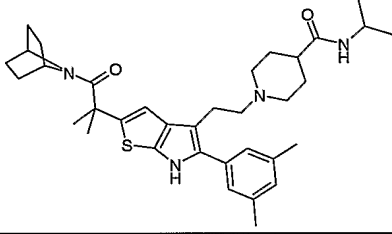
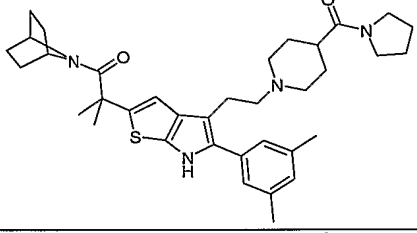
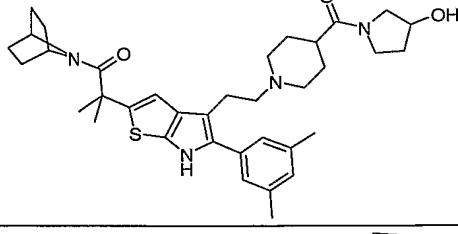
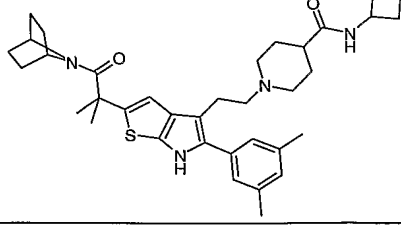
Yield : 93%

$^1\text{H}$  NMR ( $\text{DMSO-d}_6$ , AcOH) : 1.30 (m, 4H); 1.40-1.70 (m, 4H); 1.53 (s, 6H); 1.80-2.00 (m, 4H); 2.05 (m, 2H); 2.34 (s, 6H); 2.65 (m, br, 1H); 3.14 (m, 2H); 3.27 (m, 2H); 3.30-3.60 (m, 2H); 4.10 (m, br, 1H); 4.50 (m, br, 1H); 6.96 (m, 2H); 7.09 (m, 2H).

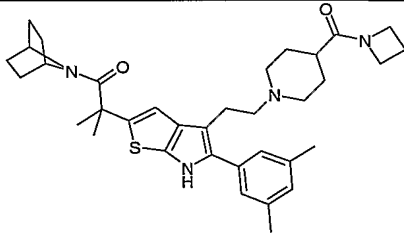
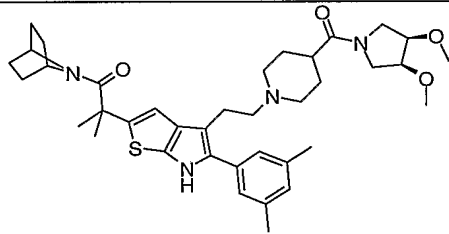
**Examples 36.1-36.8**

Following a procedure similar to that described in Example 36 the compounds of table 36 were prepared.

**Table 36**

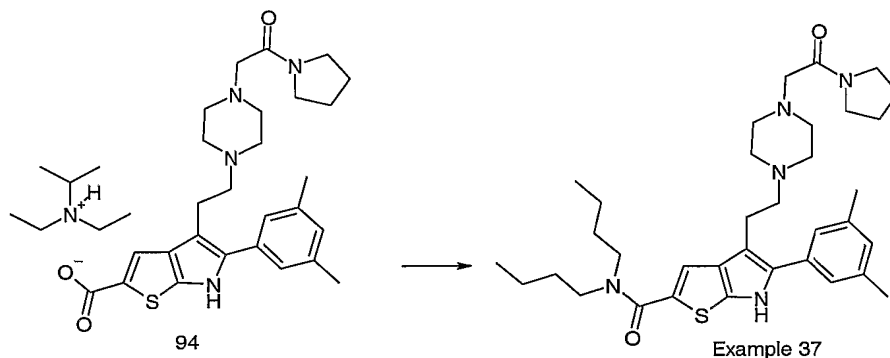
Example		MS-ESI
36.1		615 [M+H] <sup>+</sup>
36.2		587 [M+H] <sup>+</sup>
36.3		589 [M+H] <sup>+</sup>
36.4		601 [M+H] <sup>+</sup>
36.5		617 [M+H] <sup>+</sup>
36.6		601 [M+H] <sup>+</sup>

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Example		MS-ESI
36.7		587 [M+H] <sup>+</sup>
36.8		661 [M+H] <sup>+</sup>

**Example 37**

2-[N,N-Dibutylaminocarbonyl]-4-[2-(4-{pyrrolidin-1-ylcarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole



5

To a solution of **94** (0.10 g ; 0.161 mmol), dibutylamine (0.062 g ; 0.483 mmol) and DIPEA (0.062 g ; 0.483 mmol) in DMF (1 ml) at room temperature, was added solid HATU (0.183 g ; 0.483 mmol) in one portion. The reaction mixture was allowed to stand for 1 hour after which HPLC showed no remaining starting material. The reaction mixture was purified by preparative LCMS (standard basic system) to afford example **37** (0.018 g) as a beige solid.

10

Yield: 18%

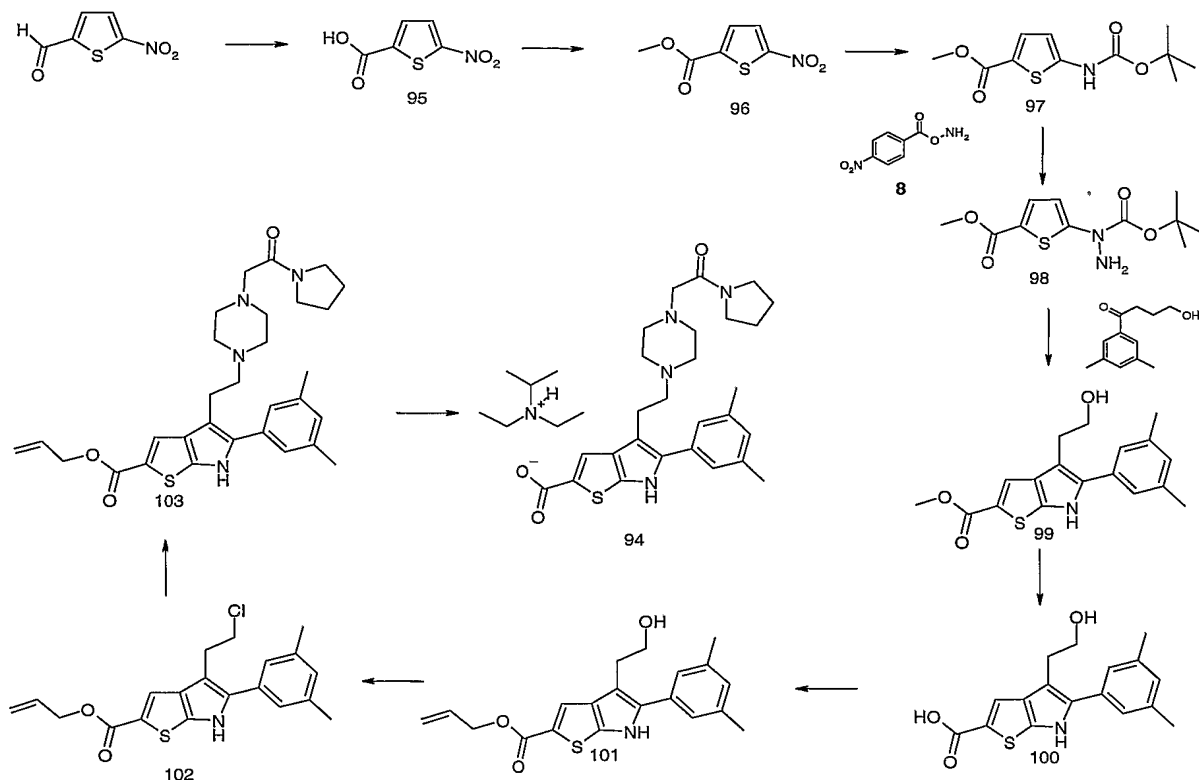
MS-ESI: 606 [M+H]<sup>+</sup>

<sup>1</sup>H NMR ( CDCl<sub>3</sub> ) 0.96 (t, 6H); 1.34-1.43 (m, 4H); 1.65-1.73 (m, 4H); 1.85 (m, 2H); 1.96 (m, 2H); 2.37 (s, 6H); 2.5-2.73 (m, 8H); 2.97 (m, 2H); 3.13 (s, 2H); 3.46-3.60 (m, 4H); 6.94 (s, 1H); 7.08 (s, 2H); 7.40 (s, 1H); 8.27 (s, 1H).

15

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The intermediate **94** was prepared as follows:



To a stirred solution of potassium dichromate (35.1 g ; 143 mmol) in 5N H<sub>2</sub>SO<sub>4</sub> (375 ml) at 0°C, was added solid 2-formyl-5-nitrothiophene (50.0 g ; 318 mmol) . The resulting suspension was heated to 100°C for 1 hour after which HPLC showed no remaining starting material. The reaction mixture was cooled to room temperature, diluted with water (300 ml) and the resulting precipitate collected by filtration, washed with water (5 x 200 ml) and dried to a constant weight in a vacuum oven at 40°C to afford **95** (39.5 g) as a light green solid.

Yield: 72%

<sup>1</sup>H NMR ( DMSO-d<sub>6</sub> ) 7.70 (d, 1H) ; 8.09 (d, 1H).

To a stirred solution of **95** (40.0 g; 230 mmol) in DMF-acetone (1:5, 200 ml) at -10°C, were added potassium carbonate (95.8 g; 694 mmol) followed by dimethylsulfate (43.6 g; 346 mmol) dropwise over 10 minutes. The acetone was removed by evaporation and the resulting suspension was stirred at room temperature for 4 hours after which HPLC showed no remaining starting material. The reaction mixture was cooled to 5°C and water (1 l) was added affording a thick precipitate, which was collected by filtration, washed with water (2 x 200 ml) and dried to a constant weight in a vacuum oven to afford **96** (38.3 g) as a beige solid.

Yield: 89%

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$^1\text{H}$  NMR (DMSO- $d_6$ ) 3.85 (s, 3H) ; 7.74 (d, 1H) ; 8.21 (d, 1H).

To a stirred solution of **96** (35 g; 187 mmol) in MeOH (400 ml) was added a suspension of 10% palladium on carbon (30 g) in AcOH (100 ml). The resulting suspension was exposed to 1 atmosphere of hydrogen for 8 hours after which HPLC showed no remaining starting material. The catalyst was removed by filtration through a pad of Celite and the filtrate was evaporated to dryness and the residue purified by flash chromatography on silica gel eluting with DCM-MeOH (98:2) to afford the amine (11.4 g) as an off-white solid, which was used immediately in the next step. To a stirred solution of the amine (11.4 g; 72.9 mmol) in THF (20 ml) was added di-tert-butylidicarbonate ((Boc) $_2$ O) (17.5 g; 80.2 mmol). The resulting solution was heated to reflux for 3 days after which HPLC showed no remaining starting material. The reaction mixture was evaporated to dryness and the residue obtained was triturated with diethyl ether (100 ml). The resulting precipitate was collected by filtration, washed with diethyl ether (2x50 ml) and dried to a constant weight to afford **97** (15.1 g) as an off-white crystalline solid.

Yield: 32%

MS-ESI: 258 [M+H] $^+$

$^1\text{H}$  NMR (DMSO- $d_6$ ) 1.53 (s, 9H), 3.74 (s, 3H) ; 6.55 (d, 1H) ; 7.57 (d, 1H).

To a stirred solution of **97** (13.2 g; 51.4 mmol) in DMF at  $-10^\circ\text{C}$  in an acetone-ice bath, was added a 60% (w/w) suspension of sodium hydride in mineral oil (2.26 g; 56.5 mmol). The resulting orange suspension was allowed to warm to room temperature and stirred for 1 hour. The reaction mixture was cooled again to  $-10^\circ\text{C}$ , and a solution of **8** (10.3 g; 56.5 mmol) in DMF (50 ml) over a period of 10 minutes. During the addition of the last 10 ml the suspension thickened and diethyl ether (200 ml) was added to mobilise the suspension. The resulting suspension was stirred for a further 2 hours at room temperature after which HPLC showed no remaining starting material. The precipitate was collected by filtration, washed with diethyl ether (3 x 100 ml) and the filtrate was washed with water (3 x 100 ml), dried over magnesium sulfate and evaporated to afford an orange oil. The oil was dissolved in diethyl ether (300 ml), cooled to  $0^\circ\text{C}$  and a 4.0M solution of HCl in 1,4-dioxane was added over a period of 10 minutes. The resulting thick white precipitate was collected by filtration, washed with diethyl ether (2 x 50 ml) and dried to a constant weight to afford **98** (9.63 g) as a white solid.

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Yield: 61%

MS-ESI: 273 [M+H]<sup>+</sup>

To a stirred solution of **98** (10.0 g; 32.5 mmol) and **22** (7.85 g; 48.7 mmol) in 2-butanol at room temperature, was added zinc chloride (6.57 g; 48.7 mmol). The resulting suspension was heated at 110°C for 3 hours. The reaction mixture was evaporated to dryness and the residue was purified by flash chromatography on silica gel eluting with DCM-acetonitrile (4:1) to afford **99** (7.1 g) as a beige solid.

Yield: 66%

10 MS-ESI: 330 [M+H]<sup>+</sup>

To a stirred solution of **99** (7.1 g; 21.5 mmol) in ethanol (50 ml) was added a solution of NaOH (4.3 g; 107 mmol) in water (22 ml). The resulting solution was heated at 70°C for 1 hour after which HPLC showed no remaining starting material. The ethanol was removed on a rotary evaporator and to the remaining concentrate at 5°C was added, with rapid agitation, concentrated HCl over period of 10 minutes. The resulting precipitate was collected by filtration, washed with water (3 x 100 ml) and dried to a constant weight in a vacuum oven at 40°C to afford **100** (5.81 g).

Yield: 86%

20 MS-ESI: 316 [M+H]<sup>+</sup>

To a stirred suspension of **100** (5.81 g; 18.4 mmol) and potassium carbonate (3.31 g; 24.0 mmol) in DMF (100 ml) at 0°C, was added dropwise neat allyl bromide (2.45 g; 20.5 mmol) over a period of 10 minutes. The reaction mixture was stirred at room temperature for a further 4 hours after which HPLC showed no remaining starting material. The reaction mixture was triturated with water (300 ml) affording an oil. The liquid was removed by decantation and the oily residue dissolved in diethyl ether (300 ml), washed with water (3 x 100 ml), dried over magnesium sulfate and evaporated to afford **101** (5.84 g; 89.4%) as a beige foam which was used without further purification.

30 Yield: 89%

MS-ESI: 355 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 2.36 (s, 6H); 3.07 (t, 2H); 3.94 (t, 2H); 4.82 (d, 2H); 5.28 (dd, 1H); 5.42 (dd, 1H); 5.98-6.08 (m, 1H); 6.97 (s, 1H); 7.12 (s, 2H); 7.84 (s, 1H); 8.35 (s, 1H).

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To a stirred solution of **101** (5.44 g; 15.4 mmol) in acetonitrile (50 ml) at 0°C, were added CCl<sub>4</sub> (5 ml) followed by triphenylphosphine (4.49 g; 16.9 mmol). The resulting orange solution was allowed to warm to room temperature and stirred for 4 hours after which HPLC  
5 showed no remaining starting material. The reaction mixture was evaporated to dryness to afford an orange residue, which was purified by flash chromatography on silica gel eluting with DCM to afford **102** (5.02 g) as an orange foam.

Yield: 88%

MS-ESI: 371 [M+H]<sup>+</sup>

10 <sup>1</sup>H NMR ( CDCl<sub>3</sub> ) 2.39 (s, 6H); 3.25 (t, 2H); 3.75 (t, 2H); 4.83 (d, 2H); 5.32 (dd, 1H); 5.44 (dd, 1H); 6.01-6.12 (m, 1H); 7.03 (s, 1H); 7.08 (s, 2H); 7.86 (s, 1H); 8.35 (s, 1H).

To a stirred solution of **102** (4.20 g; 11.3 mmol) in DMA (20 ml) were added sodium iodide (1.69 g ; 11.3 mmol), potassium carbonate (2.35 g ; 17.0 mmol) and 1-  
15 pyrrolidinocarbonylmethylpiperazine (3.35 g; 17.0 mmol). The resulting suspension was heated at 85°C for 3 hours after which HPLC showed no remaining starting material. The reaction mixture was allowed to cool to room temperature and triturated with water (100 ml) affording a thick beige precipitate which was collected by filtration, washed with water (3 c 20 ml) and dried to a constant weight in a vacuum oven at 40°C to afford **103** (6.03 g) which  
20 was used without further purification.

Yield: 100%

MS-ESI: 535 [M+H]<sup>+</sup>

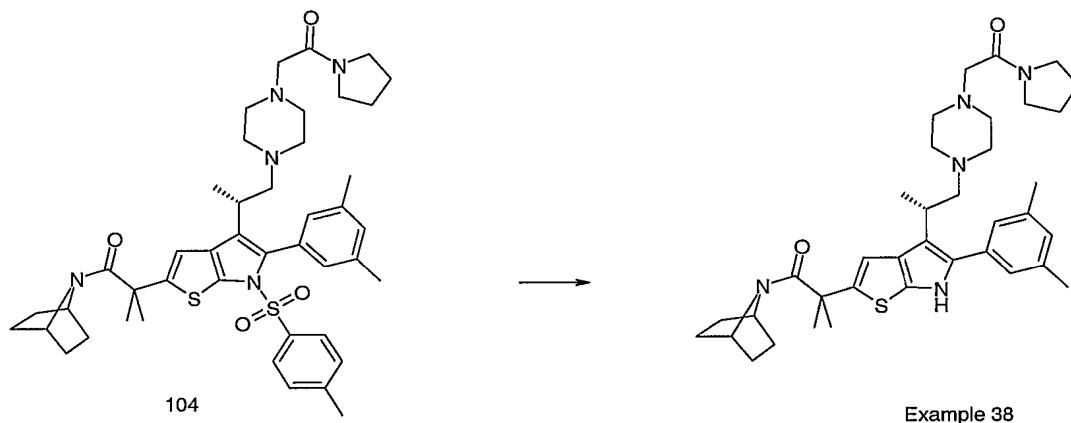
To a stirred solution of **103** (6.93 g ; 11.3 mmol) in THF (60 ml) at room temperature was  
25 added morpholine (0.984 g ; 11.30 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (3.91 g ; 3.89 mmol). The reaction mixture was stirred at room temperature for 3 hours after which HPLC showed no remaining starting material. The reaction mixture was evaporated to dryness and the residue was dissolved in MeOH (10 ml) and DIPEA (5 ml) was added. The resulting solution was evaporated to dryness to afford an orange oil. Toluene (10 ml) was added and the residue was  
30 evaporated to dryness again. The resulting orange oil was triturated with diethyl ether (100 ml) affording a grey precipitate, which was collected by filtration, washed with diethyl ether (2 x 10 ml) and dried to a constant weight to afford **94** (5.50 g) which was used without further purification.

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Yield: 78%

MS-ESI: 495 [M+H]<sup>+</sup>**Example 38**

- 5 **2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-**  
**4-[1S-methyl-2-(4-{pyrrolidin-1-ylcarbonylmethyl}piperidin-1-yl)ethyl]-5-(3,5-**  
**dimethylphenyl)-6H-thieno[2,3-b]pyrrole**



- To a stirred solution of **104** (0.27 g; 0.345 mmol) in MeOH (5 ml) at room temperature, was  
 10 added solid magnesium powder (0.083 g; 3.45 mmol). The resulting suspension was stirred  
 vigorously for 6 hours. The reaction mixture was cooled to 5°C and a saturated solution of  
 ammonium chloride (2 ml) was added. The resulting gel was mobilised with MeOH (20 ml)  
 and filtered. The filtrate was evaporated to dryness and the residue dissolved in DMF (1 ml)  
 and purified by preparative LCMS (standard basic system) to afford example **38** (0.132 g) as a  
 15 beige solid.

Yield: 61%

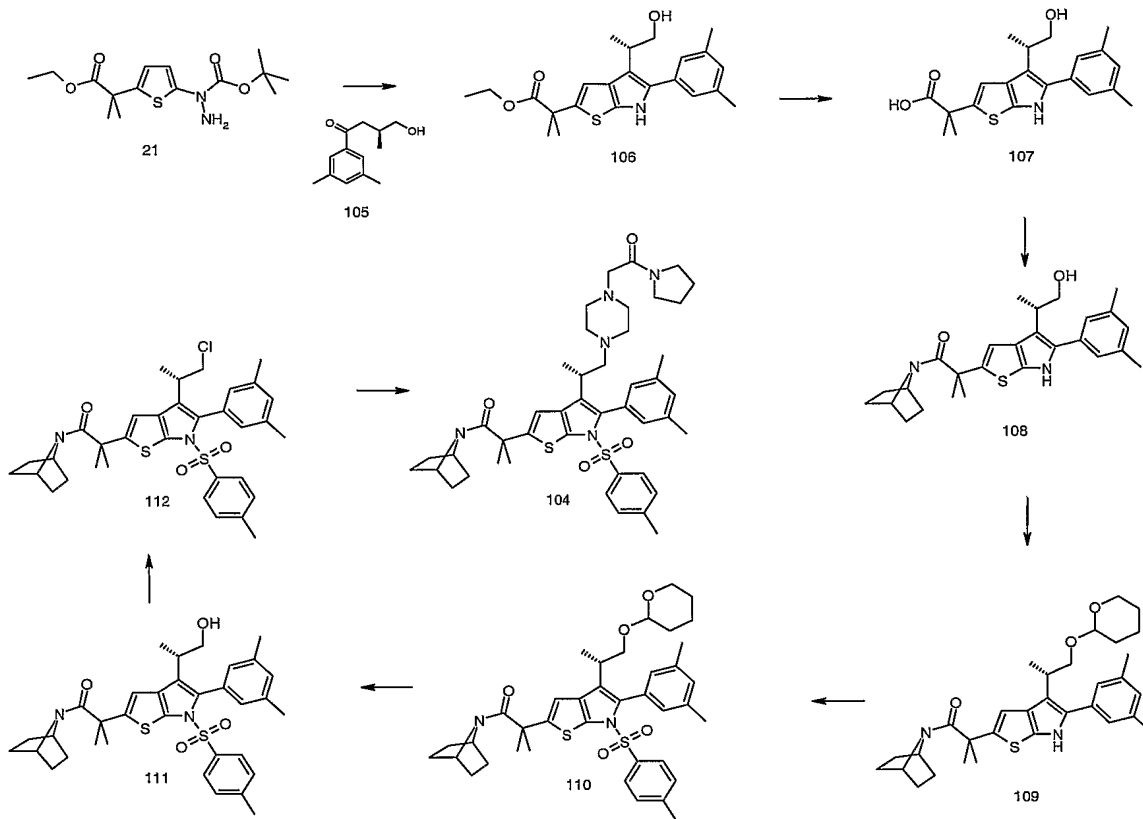
MS-ESI: 630 [M+H]<sup>+</sup>

- <sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.21–1.42 (m, 7H); 1.45 – 1.75 (m, 12H); 1.85 (m, 2H); 1.93 (m, 2H);  
 2.36 (s, 6H); 2.40–2.69 (m, 8H); 3.05 (m, 2H); 3.26 (m, 1H); 3.48 (m, 4H); 4.08 (br s, 1H);  
 20 4.73 (br s, 1H); 6.75 (s, 1H); 6.94 (s, 1H); 7.07 (s, 2H); 8.08 (s, 1H).



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Intermediate **104** was prepared as follows:



To a stirred solution of **105** (28.6 g; 139 mmol) in 2-butanol (250 ml) at 110°C was added **21** (46.0 g; 126.4 mmol) over a period of 30 minutes. The reaction mixture was maintained at 110°C for 2 hours. The reaction mixture was cooled to room temperature and zinc chloride (25.8 g; 190 mmol) was added. The resulting dark brown solution was heated at 110°C for a further 3 hours after which HPLC showed no remaining starting material. The solvent was removed on a rotary evaporator and the dark brown residue purified by flash chromatography on silica gel eluting with DCM-ethyl acetate (9:1) to afford **106** (14.5 g) as a beige foam.

Yield: 29%

MS-ESI: 400 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.15 (t, 3H); 1.33 (d, 3H); 1.71 (s, 6H); 2.33 (s, 6H); 3.05 (m, 1H); 4.06 (m, 2H); 4.60 (t, 1H); 6.87 (s, 1H); 6.93 (s, 1H); 7.07 (s, 1H).

To a stirred solution of **106** (8.00 g; 20.1 mmol) in ethanol (200 ml) was added an aqueous solution of 1N NaOH (100 ml). The resulting solution was heated at 70°C for 3 hours after which HPLC showed no remaining starting material. The ethanol was removed on a rotary evaporator and the remaining aqueous solution was cooled to 5°C and acidified to pH 1 by the

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addition of concentrated HCl.. The resulting precipitate was collected by filtration, washed to a neutral pH with water (5 x 50 ml) and dried to a constant weight to afford **107** (7.46 g) as a brown solid which was used without further purification.

Yield: 100%

5 MS-ESI: 372 [M+H]<sup>+</sup>

<sup>1</sup>H NMR ( CDCl<sub>3</sub> ) 1.32 (d, 3H); 1.73 (s, 6H); 2.33 (s, 6H); 3.26 (m, 1H); 3.80 (m, 3H); 6.94 (overlapping s, 2H); 7.08 (s, 2H); 8.12 (s, 1H).

To a stirred solution of the **107** (7.46 g; 20.0 mmol) in DCM (200 ml) at 0°C, were added  
10 DIPEA (10.4 g; 80.0 mmol) and **27.HCl** (2.64 g ; 20.0 mmol). Solid HATU (11.5 g; 30.2 mmol) was then added portionwise over a period of 5 minutes. The resulting solution was allowed to warm to room temperature and stirred for 1 hour after which HPLC showed no remaining starting material. The reaction mixture was diluted with DCM (100 ml), washed with 1N HCl (2 x 20 ml), water (2 x 20 ml), dried over magnesium sulfate and evaporated to  
15 dryness affording **108** (7.46 g) as a beige solid which was used without further purification.

Yield: 83%

MS-ESI: 451 [M+H]<sup>+</sup>

To a stirred solution of **108** (7.6 g; 16.9 mmol) in THF (50 ml) at room temperature was  
20 added pyridinium p-toluenesulfonate (PPTS) (0.850 g; 3.4 mmol) and 3,4-dihydropyran (DHP) (4.62 g; 0.7 mmol). The resulting solution was heated to reflux for 3 hours after which HPLC showed no remaining starting material. The solvent was removed by evaporation and the residue purified by flash chromatography on silica gel eluting with DCM-ethyl acetate (4:1) to afford **109** (7.20 g).

25 Yield: 80%

MS-ESI: 535 [M+H]<sup>+</sup>

To a stirred solution of **109** (7.0 g; 13.1 mmol) in THF (100 ml) at -10°C was added a 60% (w/w) suspension of sodium hydride in mineral oil (0.682 g; 17.0 mmol) followed by solid p-  
30 toluenesulfonyl chloride (2.75 g; 14.4 mmol) over a period of 10 minutes. The reaction mixture was allowed to warm to room temperature and stirred for 3 hours after which HPLC indicated a complete conversion to **110**. Concentrated HCl was added dropwise and the resulting solution was stirred for a further 2 hours at room temperature after which HPLC

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indicated a completed conversion of **110** to **111**. The solvent was removed on a rotary evaporator and the residue was partitioned between water (100 ml) and DCM (300 ml). The organic layer was washed with a saturated aqueous solution of sodium bicarbonate (100 ml), brine (2 x 50 ml), dried over magnesium sulfate and evaporated to dryness to afford a white foam which. The foam was triturated with diethyl ether (30 ml) and the resulting mobile solid was collected by filtration, washed with diethyl ether (4 x 10 ml) and dried to a constant weight in a vacuum oven at 40°C to afford **111** (2.12 g), which was used without any further purification.

Yield: 27%

10 MS-ESI: 605 [M+H]<sup>+</sup>

<sup>1</sup>H NMR ( DMSO-d<sub>6</sub> ) 1.06 (d, 3H); 1.20–1.50 (m, 8H); 1.57 (s, 6H); 2.26 (s, 6H); 2.50 (m, 1H); 3.05 (m, 2H); 3.26 (m, 1H); 3.48 (m, 4H); 4.00 (br s, 1H); 4.50 (br s, 1H); 6.65 (br s, 1H); 6.73 (br s, 1H); 6.85 (s, 1H); 7.06 (s, 1H); 7.22 (d, 2H); 7.34 (d, 2H).

15 To a stirred solution of **111** (1.0 g; 1.66 mmol) in acetonitrile (5 ml) at room temperature was added CCl<sub>4</sub> (0.5 ml) followed by triphenylphosphine (0.482 g; 1.82 mmol). The resulting suspension was stirred at room temperature for 3 hours after which HPLC indicated no remaining starting material. The solid was collected by filtration, washed with cold acetonitrile and dried to a constant weight to afford **112** (0.542 g) as a white solid.

20 Yield: 53%

MS-ESI: 623 [M+H]<sup>+</sup>

To a stirred suspension of **112** (0.45 g; 0.721 mmol), potassium carbonate (0.50 g; 3.62 mmol) and sodium iodide (0.106 g; 0.721 mmol) in DMA (2 ml) at room temperature, was added 1-pyrrolidinocarbonylmethyl piperazine (0.712 g; 3.62 mmol). The resulting suspension was heated at 110°C for 12 hours after which HPLC showed no remaining starting material. The reaction mixture was triturated with water (20 ml) and the resulting beige precipitate was collected by filtration, washed with water (2 x 10 ml) and dried to a constant weight. The resulting solid was dissolved in DCM (3 ml) and purified by flash chromatography eluting with DCM-MeOH (98:2) to afford **104** (0.270 g) as a beige solid.

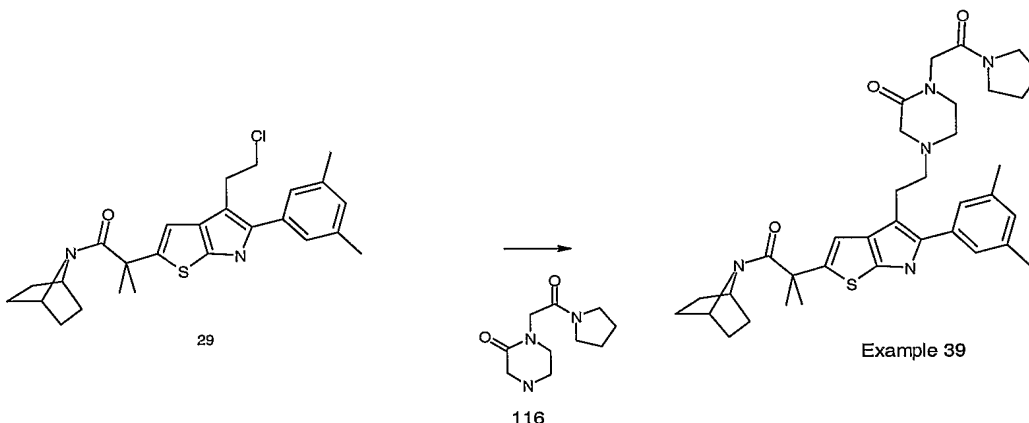
Yield: 48%

MS-ESI: 784 [M+H]<sup>+</sup>

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**Example 39**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-  
4-[2-(3-oxo-4-{pyrrolidin-1-ylcarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-  
dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**



5

To a stirred solution of 22 (0.30 g; 0.66 mmol) in DMA (3 ml) at room temperature were added potassium carbonate (0.27 g; 1.98 mmol) and 134 (0.42 g; 1.98 mmol). The resulting suspension was heated to 130°C for 8 hours after which HPLC showed no remaining starting material. The reaction mixture was cooled to room temperature and triturated with water (10 ml). The resulting precipitate was collected by filtration, washed with water (2 x 5 ml) and dried. The resulting beige solid was dissolved in DCM (3 ml) and purified by flash chromatography on silica gel eluting with DCM-methanol (95:5) to afford **Example 39** (0.12 g) as a white foam.

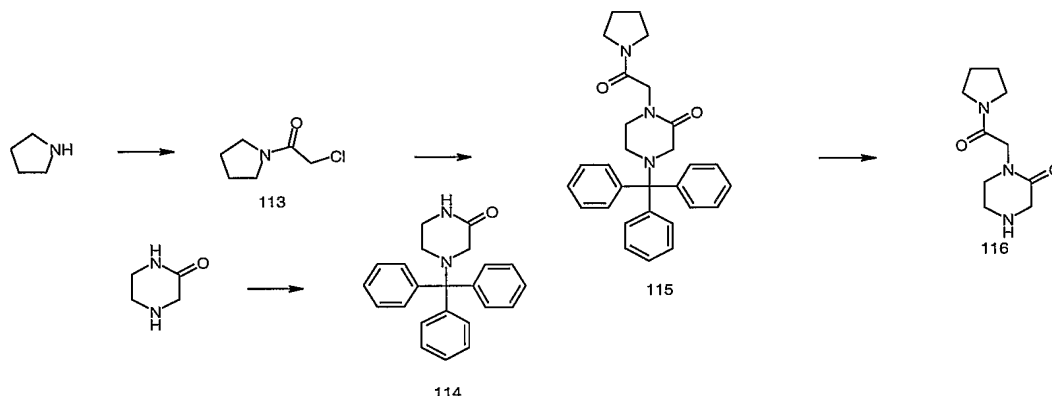
Yield: 25%

15 MS-ESI: 630 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.25-1.39 (m, 4H); 1.45-1.76 (m, 10H); 1.84 (m, 2H); 1.95 (m, 2H); 2.37 (s, 6H); 2.72 (m, 2H); 2.79 (m, 2H); 2.96 (m, 2H); 3.28 (s, 2H); 3.38 (m, 6H); 4.12 (2 overlapping s, 3H); 4.75 (br s, 1H); 6.73 (br s, 1H); 6.94 (s, 1H); 7.04 (s, 2H); 8.14 (s, 1H).

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The intermediate **116** was prepared as follows:



To a stirred solution of pyrrolidine (1.0 g; 14.1 mmol) and triethylamine (1.57 g; 15.5 mmol) in DCM (20 ml) at  $-10^{\circ}\text{C}$ , was added chloroacetyl chloride (1.52 g; 13.4 mmol) over a period of 10 minutes. The reaction mixture was diluted with DCM (20 ml) and washed with 2N HCl (2 x 10 ml), water (2 x 10 ml) and dried over magnesium sulfate. The organic layer was evaporated to dryness to afford **113** (1.30 g).

Yield: 66%.

$^1\text{H}$  NMR (  $\text{CDCl}_3$  ) 1.88 (m, 4H); 1.95 (m, 2H); 3.50 (m, 4H) ; 4.03 (s, 2H) .

10

To a stirred solution of piperazin-2-one (2.0 g; 19.9 mmol) and triethylamine (2.42 g; 23.9 mmol) in THF (20 ml) at  $-10^{\circ}\text{C}$  in an acetone-ice bath, was added solid triphenylmethylchloride (5.57 g; 19.9 mmol) over a period of 5 minutes. The reaction mixture was allowed to warm to room temperature and stirred over night after which HPLC showed no remaining starting material. The solvent was removed on a rotary evaporator and the resulting white solid washed with diethyl ether (3 x 50 ml), water (4 x 50 ml) and dried to a constant weight in a vacuum oven to afford **114** (6.8 g) as a white solid.

Yield: 100%.

$^1\text{H}$  NMR (  $\text{CDCl}_3$  ) (  $\delta$  ppm) 2.50 ( m, 2H ) ; 3.11 ( m, 2H ) ; 3.46 ( s, 2H ) ; 5.93 ( s, 1H ) ; 7.21 (m, 3H) ; 7.31 ( m, 7H) ; 7.35 ( m, 5H).

20

To a stirred solution of **114** (1.0 g; 5.84 mmol) in DMF (50 ml), was added a 60% (w/w) suspension of NaH in mineral oil (0.26 g; 6.43 mmol) at  $0^{\circ}\text{C}$ . The reaction mixture was allowed to stir for 1 hour at  $0^{\circ}\text{C}$  before **113** (0.864 g; 5.84 mmol) was added portionwise over a period of 5 minutes. The resulting solution was allowed to warm to room temperature and stirred for an additional hour. The reaction mixture was cooled to  $0^{\circ}\text{C}$ , triturated with water

**- 165 -**

(100 ml) and the resulting precipitate was collected by filtration, washed with water (3 x 20 ml) and dried to a constant weight to afford **115** (2.20 g) as a white solid which was used without further purification.

Yield: 83%.

- 5  $^1\text{H}$  NMR (  $\text{CDCl}_3$  ) 1.83 (m, 2H); 1.97 (m, 2H); 2.46 (m, 2H); 3.15 (m, 2H); 3.46 (m, 4H); 3.49 (m, 2H); 4.12 (s, 2H); 7.17 (m, 3H); 7.27 (m, 7H); 7.46 (m, 5H).

To a stirred solution of **115** (2.2 g; 4.80 mmol) in MeOH (20 ml) at room temperature, was added concentrated HCl (2 ml) in one portion. The reaction mixture was stirred at room  
 10 temperature for 1 hour after which TLC ( $\text{SiO}_2$ , DCM) showed no remaining starting material. The solvent was removed on a rotary evaporator to afford an oily orange residue. Toluene (50 ml) was added and the resulting suspension was evaporated to dryness to afford a thick orange oil which was dried under high vacuum to afford **116** (1.2 g; 100%) as an orange foam which was used without further purification.

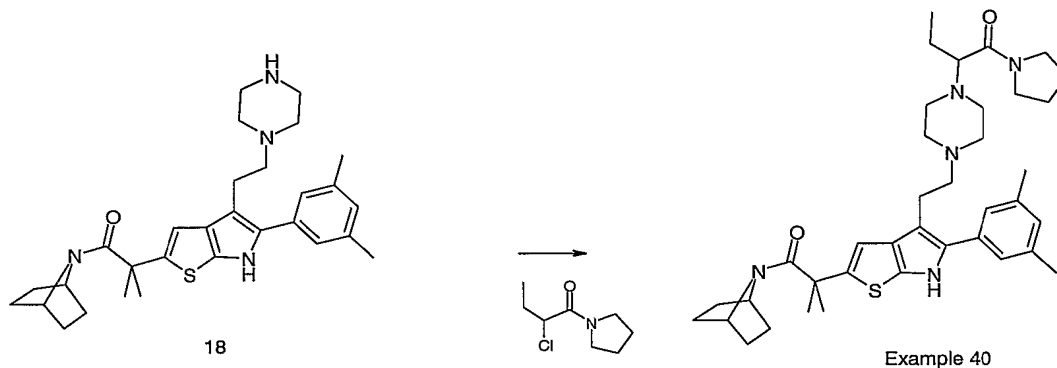
- 15 Yield: 100%

**Example 40**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-**

**4-[2-(4-{4-oxo-4-pyrrolidin-1-ylbut-3-yl}piperazin-1-yl)ethyl]-5-(3,5-**

- 20 **dimethylphenyl)-6H-thieno[2,3-b]pyrrole**



117

- To a stirred solution of **18** (0.30 g ; 0.595 mmol) in DMF (1 ml) was added **117** (0.23 g; 1.19 mmol). The reaction mixture was heated at 130°C for 8 hours after which HPLC showed no remaining starting material. The reaction mixture was purified by flash chromatography on  
 25 silica gel eluting with DCM-MeOH (96:4) to afford example **40** (0.09 g) as a beige solid.

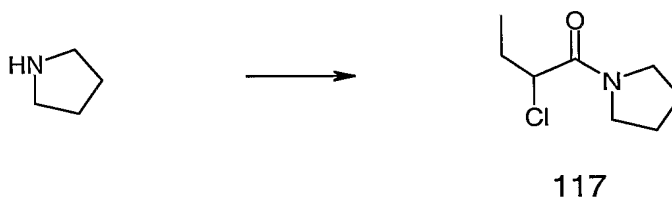
Yield: 24%

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MS-ESI: 644  $[M+H]^+$ 

$^1\text{H}$  NMR (  $\text{CDCl}_3$  ) 0.83 (t, 3H); 1.17 (m, 2H); 1.25-1.39 (br m, 4H); 1.45-1.76 (m, 8H); 1.84 (m, 2H); 1.91 (m, 6H); 2.33 (s, 6H); 2.46-2.79 (m, 8H); 2.94 (m, 2H); 3.14 (m, 1H); 3.45 (m, 3H); 3.65 (m, 1H); 4.10 (br s, 1H); 4.74 (br s, 1H); 6.73 (s, 1H); 6.92 (s, 1H); 7.04 (s, 2H); 8.16 (s, 1H).

The intermediate **117** was prepared as follows:

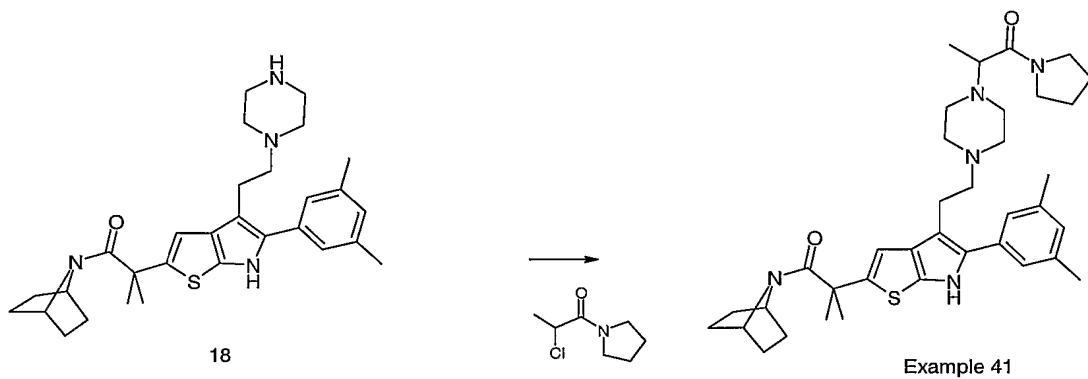


To a stirred suspension of pyrrolidine (1.0 g; 14.1 mmol) and triethylamine (1.57 g; 15.5 mmol) in DCM (20 ml) at  $-10^\circ\text{C}$ , was added 2-chlorobutyryl chloride (1.80 g; 12.7 mmol) over a period of 10 minutes. The reaction mixture was allowed to warm to room temperature and stirred for an additional hour after. The reaction mixture was diluted with DCM (20 ml) and washed with 2N HCl (10 ml), water (2 x 10 ml), dried over magnesium sulfate and evaporated to dryness on a rotary evaporator to afford **117** (1.2 g).

Yield: 54%

$^1\text{H}$  NMR (  $\text{CDCl}_3$  ) 1.03 (t, 3H) ; 1.61 (m, 2H) ; 1.84-2.01 (m, 4H) ; 2.10 (m, 1H) ; 3.45 (m, 2H) ; 3.66 (m, 1H) ; 4.21 (m, 1H).

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**Example 41****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-****4-[2-(4-{3-oxo-3-pyrrolidin-1-ylprop-2-yl}piperazin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-****6H-thieno[2,3-b]pyrrole**

5

Starting from **18** (0.40 g ; 0.794 mmol) using a similar procedure described for the synthesis of example **40**, example **41** (0.12 g) was obtained as an off-white solid.

Yield: 24%

MS-ESI: 630 [M+H]<sup>+</sup>

- 10 <sup>1</sup>H NMR ( CDCl<sub>3</sub> ) 1.19 (d, 3H); 1.20-1.40 (br m, 4H); 1.45–1.78 (m, 12H); 1.82 (m, 2H); 1.91 (m, 2H); 2.33 (s, 6H); 2.44-2.71 (m, 8H); 2.92 (m, 2H); 3.34 (m, 1H); 3.44 (m, 3H); 3.72 (m, 1H); 4.10 (br s, 1H); 4.74 (br s, 1H); 6.72 (s, 1H); 6.93 (s, 1H); 7.03 (s, 2H); 8.21 (s, 1H).

- 15 Starting from pyrrolidine (1.0 g ; 14.1 mmol) and the appropriate acid chloride using a similar procedure described for the synthesis of **117**, **118** (1.47 g) was obtained as a yellow oil.

Yield: 57%

<sup>1</sup>H NMR ( CDCl<sub>3</sub> ) 1.65 (d, 3H); 1.86 (m, 2H); 1.95 (m, 2H); 3.5 (m, 3H); 3.69 (m, 1H); 4.47 (m, 1H).

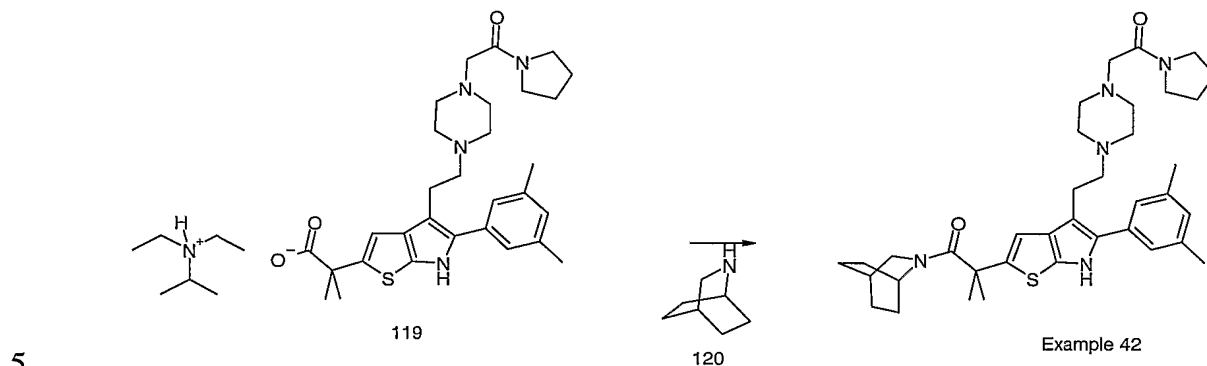
20



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**Example 42**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-  
4-[2-(4-{pyrrolidin-1-ylcarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-  
dimethylphenyl)-6H-thieno[2,3-b]pyrrole**

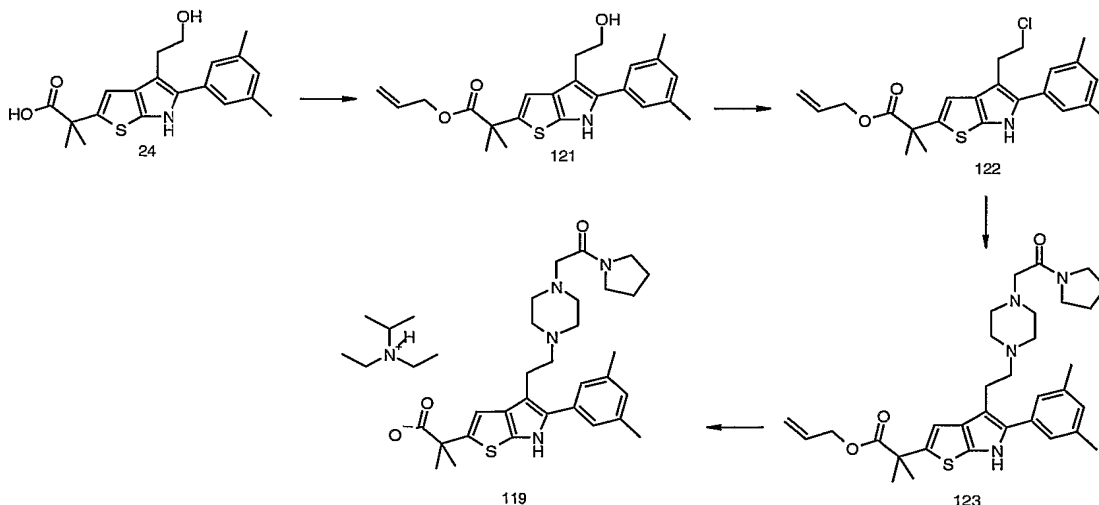


To a solution of **119** (0.20 g ; 0.30 mmol), **120.HCl** (0.123 g ; 0.901 mmol) and DIPEA (0.116 g ; 0.901 mmol) in DMF (1 ml) at room temperature, was added solid HATU (0.343 g ; 0.901 mmol) in one portion. The reaction mixture was allowed to stand for 1 hour after which HPLC showed no remaining starting material. The reaction mixture was purified by  
10 preparative LCMS (standard basic system) to afford example **42** (0.070 g) as a beige solid.

Yield: 37%

MS-ESI: 630 [M+H]<sup>+</sup>

<sup>1</sup>H NMR ( CDCl<sub>3</sub> ) 1.34-1.69 (m, 20H); 1.85 (m, 2H); 1.94 (m , 2H); 2.34 (s, 6H); 2.5–2.73 (m, 8H); 2.95 (m , 2H); 3.13 (s, 2H); 3.46-3.53 (m, 4H); 6.67 (s, 1H); 6.94 (s, 1H); 7.06 (s,  
15 2H); 8.12 (s, 1H).

The intermediate **119** was prepared as follows:

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To a stirred suspension of **24** (5.0 g; 14.0 mmol) and potassium carbonate (2.48 g; 18.0 mmol) in DMF (50 ml) at 0°C, was added dropwise neat allyl bromide (1.86 g; 15.4 mmol) over a period of 10 minutes. The reaction mixture was stirred at room temperature for a further 4  
5 hours after which HPLC showed no remaining starting material. The reaction mixture was partitioned between water (100 ml) and diethyl ether (300 ml). The organic layer was retained, washed with water (3 x 100 ml), dried over magnesium sulfate and evaporated to dryness to afford **121** (4.89 g) as a beige foam which was used without further purification.

Yield: 88%

10 MS-ESI: 397 [M+H]<sup>+</sup>

To a stirred solution of **121** (4.89 g ; 12.3 mmol) in acetonitrile (50 ml) at 0°C, were added CCl<sub>4</sub> (5 ml) followed by triphenylphosphine (4.91 g ; 18.5 mmol). The resulting orange solution was allowed to warm to room temperature and stirred for 2 hours after which HPLC  
15 showed no remaining starting material. The reaction mixture was evaporated to dryness to afford an orange residue, which was purified by flash chromatography on silica gel eluting with DCM to afford **122** (2.5 g) as an orange foam.

Yield: 49%

MS-ESI: 415 [M+H]<sup>+</sup>

20

To a stirred solution of **122** (2.50 g ; 6.04 mmol) in DMA (20 ml) were added sodium iodide (0.905 g ; 6.04 mmol), potassium carbonate (1.24 g ; 9.06 mmol) and 1-pyrrolidinocarbonylmethyl piperazine (1.79 g; 9.06 mmol). The resulting suspension was heated at 85°C for 4 hours after which HPLC showed no remaining starting material. The  
25 reaction mixture was allowed to cool to room temperature and triturated with water (100 ml) affording an oil. The water was removed by decantation and the oil dissolved in DCM (100 ml), washed with water (3 x 10 ml), evaporated to dryness on a rotary evaporator and dried to a constant weight under high vacuum to afford **123** (2.87 g) which was used without further purification.

30 Yield: 82%

MS-ESI: 577 [M+H]<sup>+</sup>

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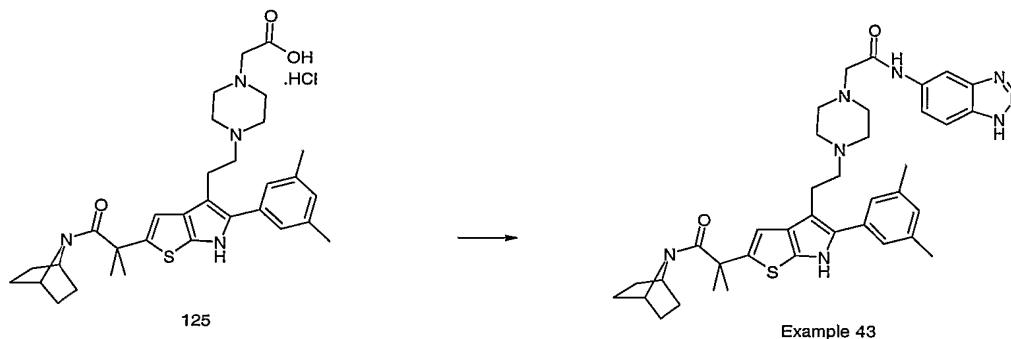
To a stirred solution of **123** (2.87 g; 4.98 mmol) in THF (40 ml) at room temperature was added morpholine (0.409 g; 4.70 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (1.63 g; 1.91 mmol). The reaction mixture was stirred at room temperature for 3 hours after which HPLC showed no remaining starting material. The reaction mixture was evaporated to dryness and the residue was dissolved in MeOH (10 ml) and DIPEA (5 ml) was added. The resulting solution was evaporated to dryness to afford an orange solid. Toluene (10 ml) was added and the residue was evaporated to dryness again. The resulting orange oil was triturated with diethyl ether (50 ml) affording a precipitate, which was collected by filtration, washed with diethyl ether (2 x 10 ml) and dried to a constant weight to afford **119** (2.74 g) as a beige solid which was used without further purification.

Yield: 83%

MS-ESI: 537 [M+H]<sup>+</sup>

**Example 43**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-(4-{1H-1,2,3-benzotriazol-5-ylaminocarbonylmethyl}piperazin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**



To a solution of **125** (0.20 g ; 0.334 mmol), 5-aminobenzotriazole (0.067 g ; 0.501 mmol) and DIPEA (0.129 g ; 1.0 mmol) in DMF (1 ml) at room temperature, was added solid HATU (0.191 g ; 0.501 mmol) in one portion. The reaction mixture was allowed to stand for 16 hours after which HPLC showed no remaining starting material. The reaction mixture was purified by preparative LCMS (standard acidic system) to afford example **43** (0.028 g) as a brown solid.

Yield: 12%

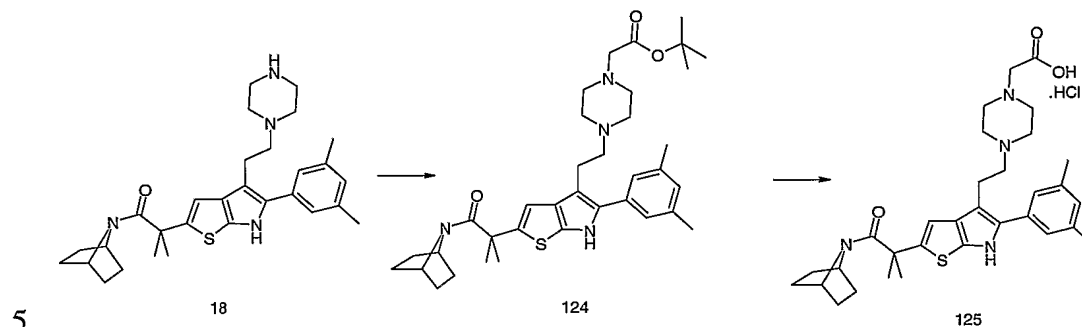
MS-ESI: 679 [M+H]<sup>+</sup>

<sup>1</sup>H NMR ( DMSO-d<sub>6</sub> ) 1.24-1.33 (m, 4H); 1.35-1.56 (m, 10H); 1.88 (m, 4H); 2.35 (s, 6H); 2.5-2.73 (m, 2H); 2.84 (m, 2H); 3.15 (s, 2H); 3.46-3.53 (m, 4H); 4.10 (br s, 1H); 4.45 (br s,

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1H); 6.81 (s, 1H); 6.92 (s, 1H); 7.09 (s, 2H); 7.43 (d, 1H); 7.86 (d, 1H); 8.32 (s, 1H); 9.94 (s, 1H); 11.26 (s, 1H).

The intermediate **125** was prepared as follows:



To a stirred suspension of **18** (6.82 g; 13.5 mmol) and potassium carbonate (2.43 g; 17.6 mmol) in DMF (20 ml) at room temperature, was added t-butyl bromoacetate (2.64 g; 13.5 mmol). The resulting orange suspension was heated at 50°C for 2 hours after which HPLC showed no remaining starting material. The reaction mixture was cooled to 0-5°C and water (300 ml) was added producing a thick precipitate, which was collected by filtration, washed with water (3 x 50 ml) and dried to a constant weight to afford **124** (7.0 g) as a beige solid.

Yield: 84%

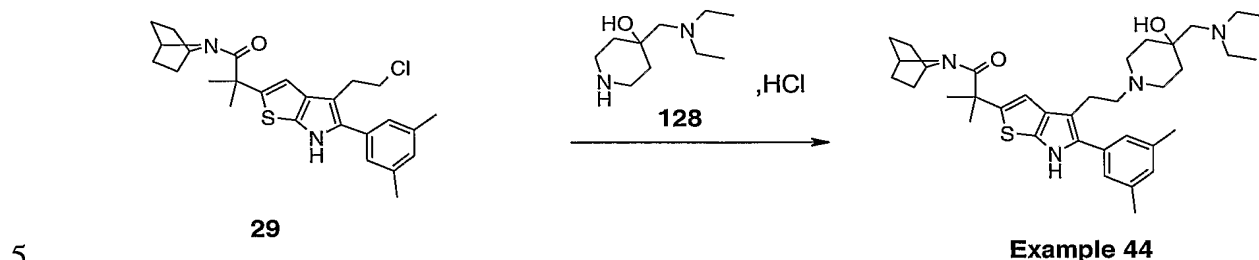
MS-ESI: 619[M+H]<sup>+</sup>

15 To a stirred solution of **124** (7.0 g; 11.3 mmol) in DCM (50 ml) at room temperature, was added concentrated HCl (10 ml). The reaction mixture was heated at 40°C for 2 hours after which HPLC showed no remaining starting material. The solvent was evaporated on a rotary evaporator to afford an orange residue. Toluene (50 ml) was added and the resulting oil suspension was evaporated to dryness and dried to a constant weight under high vacuum to afford **125** (6.77 g) as a beige foam which was used without further purification.

Yield: 100%

MS-ESI: 563 [M+H]<sup>+</sup>

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**Example 44****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-****4-[2-(4-hydroxy-4-{N,N-diethylaminomethyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-b]pyrrole**

A mixture of **29** (0.16 g; 0.35 mmol), **128** (0.153 g, 0.69 mmol), and K<sub>2</sub>CO<sub>3</sub> (0.153 g; 1.04 mmol) in acetonitrile (3 ml) and DMF (2 ml) was heated at 90°C under argon atmosphere for 3 hours. The crude mixture was purified by flash chromatography eluting with 3.5 N MeOH-NH<sub>3</sub> / methylene chloride 95/5 to give after trituration in pentane **Example 44** as a solid.

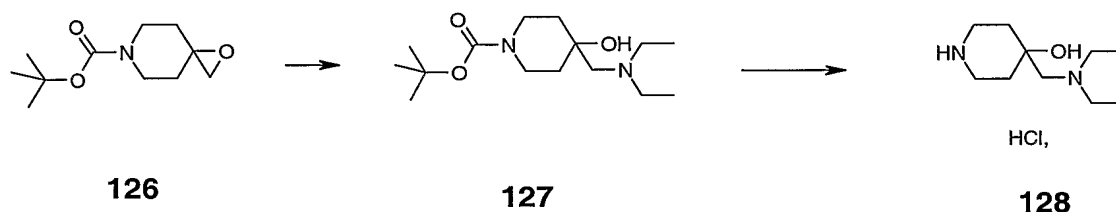
10 Yield: 51 %

MS-ESI: 605 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.01 (t, 6H); 1.20-1.44 (m, 4H); 1.50-1.70 (m, 8H); 1.62 (s, 6H); 2.35 (s, 6H); 2.37 (m, 2H); 2.45 (m, 2H); 2.59 (q, 4H); 2.69 (m, 2H); 2.72 (m, 2H); 2.97 (m, 2H); 4.1 (br s, 1H); 4.61 (br s, 1H); 4.75 (br s, 1H); 6.76 (s, 1H); 6.94 (s, 1H); 7.07 (s, 2H); 8.15 (s, 1H).

15

The starting material was prepared as follows:



A solution of **126** (0.639 g; 3 mmol) and diethylamine (0.620 ml; 6 mmol) in ethanol (5ml) was stirred overnight at ambient temperature under argon atmosphere. After evaporation to dryness, the residue was purified by flash chromatography eluting with 3.5 N MeOH-NH<sub>3</sub> / methylene chloride 95/5 to give **127** as a solid.

Yield: 86%

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 1.01 (t, 6H); 1.39 (m, 2H); 1.45 (s, 9H); 1.58 (m, 2H); 2.34 (s, 2H); 2.58 (q, 4H); 3.15 (br s, 2H); 4.85 (br s, 2H).

25

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**127** (0.465g; 1.62 mmol) was dissolved in methylene chloride (0.8ml) and dioxan (6 ml) and treated with a solution made of 12N HCl / dioxan 5/25 (4.5 ml). The mixture was stirred at ambient temperature, under argon atmosphere overnight. After evaporation to dryness, the residue was triturated in a mixture of MeOH, methylene chloride and ether to give **128** as solid.

Yield: 100%

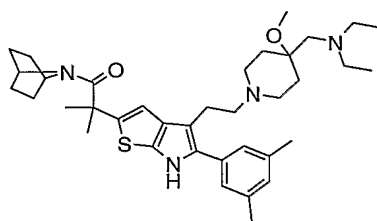
$^1\text{H}$  NMR (DMSO- $d_6$ ) 1.25 (t, 6H); 1.81 (m, 2H); 1.96 (m, 2H); 2.51 (s, 2H); 3.02–3.30 (m, 6H); 3.37 (br s, 2H).

10

**Example 45**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-**

**4-[2-(4-methoxy-4-{N,N-diethylaminomethyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole**



15

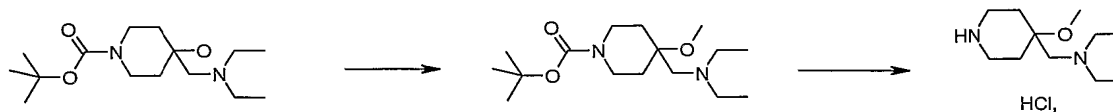
The compound was prepared using a method similar to that described in **Example 44** with amine **131** instead of amine **128**.

Yield: 72%

MS-ESI: 619 [M+H] $^+$

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) 0.97 (t, 6H); 1.20–1.40 (m, 4 H); 1.40–1.85 (m, 8H); 1.63 (s, 6H); 2.35 (s, 6H); 2.37–2.55 (m, 4H); 2.57 (q, 4H); 2.85 (m, 2H); 3.04 (m, 4H); 3.19 (s, 3H); 4.10 (br s, 1H); 4.70 (br s, 1H); 6.81 (s, 1H); 6.94 (s, 1H); 7.04 (s, 2H); 8.18 (s, 1H).

The starting material was prepared as follows:



25

**129****130****131**

To a stirred solution of **129** (0.82 g; 2.6 mmol) in THF (18 ml), was added a 60% (w/w) suspension of sodium hydride in mineral oil (0.175 g). The resulting suspension was stirred at

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room temperature for 3 minutes. Methyl iodide (0.3 ml) and 15-5 crown ether were added and the reaction mixture was stirred further overnight. After evaporation to dryness, the residue was purified by flash chromatography eluting with 3.5 N MeOH-NH<sub>3</sub> / methylene chloride 97/3 to give **130** as a solid.

5 Yield: 79%

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 0.97 (t, 6H); 1.47 (s, 9H); 1.58 (m, 2H); 1.75 (m, 2H); 2.38 (s, 2H); 3.05 (br s, 2H); 3.21 (s, 3H); 3.85 (br s, 2H).

**130** (0.680 g; 2.26 mmol) was dissolved in methylene chloride (1.2 ml) and dioxan (9 ml) and  
10 treated with a solution made of 12N HCl / dioxan 5/25 (5.5 ml). The mixture was stirred at ambient temperature, under argon atmosphere overnight. After evaporation to dryness, the residue was triturated in a mixture of MeOH, methylene chloride and ether to give **131** as solid.

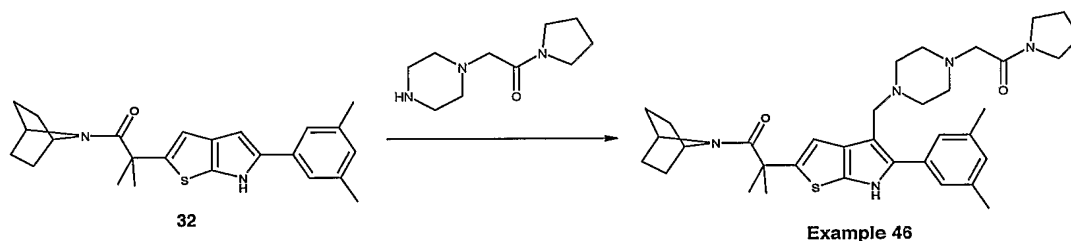
Yield: 100%

15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) 1.24 (t, 6H); 1.80 (m, 2H); 2.08 (m, 2H); 2.92 (m, 2H); 3.20 (s, 3H); 3.10–3.30 (m, 8H).

#### Example 46

2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-

20 4-[4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-ylmethyl]-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole



To a mixture of 1-[2-(Piperazin)-1-yl]acetylpyrrolidine (0.065 g; 0.33 mmol) and formaldehyde (0.013 g; 0.16 mmol) in acetic acid (5 ml) was added **32** (0.065 g; 0.17 mmol)  
25 in dioxane (8 ml) at room temperature. After 4 hours, the crude mixture was evaporated and purified by flash chromatography eluting with a gradient 2-10% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give after trituration in ether/pentane Example **46** as a solid.

Yield: 65%

MS-ESI: 602 [M+H]<sup>+</sup>

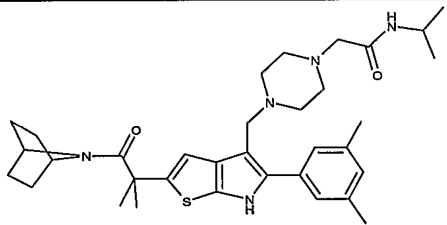
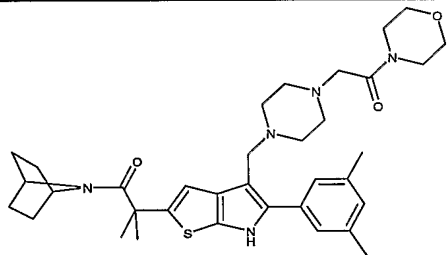
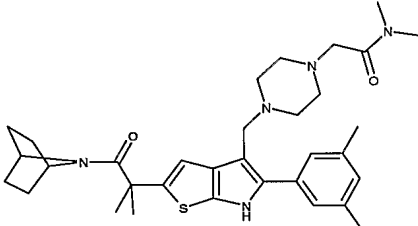
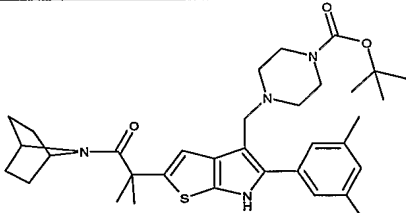
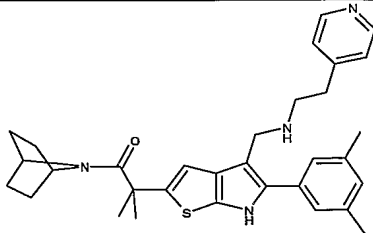
**- 175 -**

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.20-1.40 (m, 4H); 1.45-1.80 (m, 4H); 1.62 (s, 6H); 1.84 (m, 2H); 1.94 (m, 2H); 2.35 (s, 6H); 2.54 (br m, 8H); 3.10 (s, 2H); 3.45-3.52 (m, 4H); 3.54 (s, 2H); 4.14 (br m, 1H); 4.73 (br m, 1H); 6.81 (s, 1H); 6.94 (s, 1H); 7.26 (s, 2H); 8.25 (s, 1H).

**5 Examples 46.1–46.5**

Following a procedure similar to that described in **Example 46**, the compounds of **table 46** were prepared.

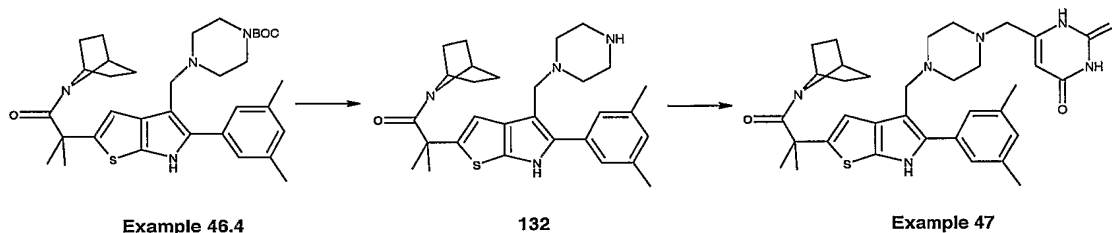
**Table 46**

Example		MS-ESI
<b>46.1</b>		590 $[\text{M}+\text{H}]^+$
<b>46.2</b>		618 $[\text{M}+\text{H}]^+$
<b>46.3</b>		576 $[\text{M}+\text{H}]^+$
<b>46.4</b>		591 $[\text{M}+\text{H}]^+$
<b>46.5</b>		527 $[\text{M}+\text{H}]^+$



**Example 47**

2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-ylmethyl)piperazin-1-ylmethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole



A mixture of **132** (0.170 g; 0.35 mmol), chloromethyluracil (0.061 g; 0.38 mmol), NaI (0.057 g; 0.38 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.053 g; 0.38 mmol) in dimethylacetamide (8 ml) was heated at 80°C under argon atmosphere for 17 hours. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 2-8% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give after trituration in ether/heptane **Example 47** as a pale brown solid.

Yield: 41%

MS-ESI: 615 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.20-1.40 (br m, 4H); 1.56 (br m, 4H); 1.63 (s, 6H); 2.36 (s, 6H); 2.50 (br m, 8H); 3.29 (s, 2H); 3.58 (s, 2H); 4.15 (br m, 1H); 4.75 (br m, 1H); 5.53 (s, 1H); 6.80 (s, 1H); 6.96 (s, 1H); 7.21 (s, 2H); 7.97 (br s, 1H); 8.25 (s, 1H); 8.53 (br s, 1H).

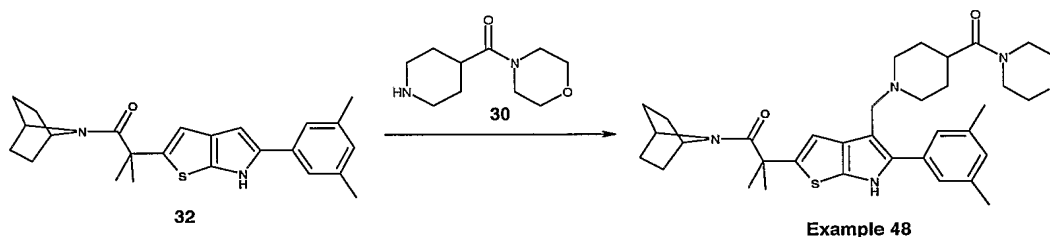
**Example 46.4** (0.878 g, 1.49 mmol) was deprotected with concentrated HCl (1.5 ml) in dioxane (15 ml) at room temperature for 4 hours. The crude mixture was evaporated, then 100 ml of 3.5 N NH<sub>3</sub> in MeOH was added, and evaporated again. The crude residue was purified by flash chromatography eluting with a gradient 0-10% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give **132**.

Yield = 100%

MS-ESI: 491 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) : 1.26 (br m, 4H); 1.45 (br m, 4H); 1.52 (s, 6H); 2.30 (s, 6H); 2.35 (m, 4H); 2.67 (m, 4H); 3.41 (m, 2H); 4.20-4.45 (br m, 2H); 6.79 (s, 1H); 6.90 (s, 1H); 7.31 (s, 2H); 11.34 (br s, 1H).

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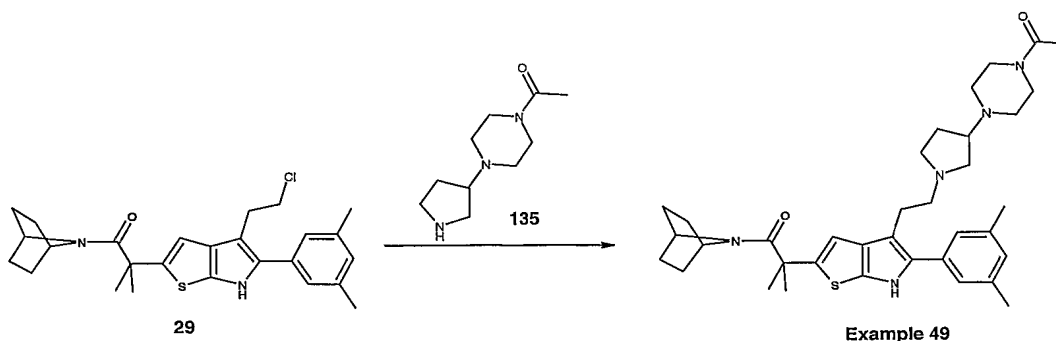
**Example 48****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[4-****(morpholinocarbonyl)piperidin-1-ylmethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-****5 *b*]pyrrole**

To a mixture of **30** (0.058 g; 0.29 mmol) and formaldehyde (0.021 g; 0.26 mmol) in acetic acid (10 ml) was added **32** (0.104 g; 0.27 mmol) in dioxane (20 ml) at room temperature. After 4 hours, the crude mixture was evaporated and purified by flash chromatography eluting with a gradient 1-5% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give after trituration in ether/pentane **Example 48** as a solid.

Yield: 98%

MS-ESI: 603 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.20-1.40 (m, 4H); 1.62 (s, 6H); 1.68 (m, 5H); 1.85 (m, 2H); 2.00 (m, 2H); 2.35 (s, 6H); 2.42 (m, 1H); 3.05 (m, 2H); 3.47 (m, 5H); 3.61 (m, 2H); 3.66 (m, 4H); 4.14 (br m, 1H); 4.73 (br m, 1H); 6.79 (s, 1H); 6.94 (s, 1H); 7.27 (s, 2H); 8.27 (s, 1H).

**Example 49****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-****(3-(4-acetylpiperazin-1-yl)pyrrolidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*****b*]pyrrole**

A mixture of **29** (0.133 g; 0.29 mmol), **135** (0.063 g, 0.32 mmol), NaI (0.048 g; 0.32 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.044 g; 0.32 mmol) in dimethylacetamide (3 ml) was heated at 85°C under argon

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atmosphere for 4 hours. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 4-8% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give after trituration in ether/pentane **Example 49** as a solid.

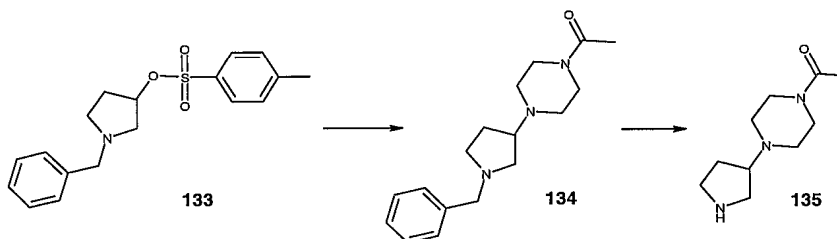
Yield: 52%

5 MS-ESI: 616 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.29 (m, 4H); 1.61 (s, 6H); 1.45-1.80 (m, 4H); 2.00 (m, 1H); 2.08 (s, 3H); 2.34 (s, 6H); 2.42 (m, 5H); 2.48 (m, 1H); 2.55 (m, 1H); 2.70 (m, 1H); 2.80 (m, 2H); 2.88 (m, 2H); 2.93 (m, 2H); 3.46 (m, 2H); 3.62 (m, 2H); 4.10 (br m, 1H); 4.75 (br m, 1H); 6.73 (s, 1H); 6.94 (s, 1H); 7.06 (s, 2H); 8.16 (s, 1H).

10

**135** was prepared as follows :



A mixture of **133** (0.461 g; 1.39 mmol) and acetyl piperazine (0.535 g; 4.17 mmol) in dimethylformamide (1 ml) was heated at reflux under argon atmosphere for 1 hour. The crude  
 15 mixture was evaporated and purified by flash chromatography eluting with a gradient 0-3% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give **134** as an oil.

Yield: 80%

MS-ESI: 288 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.73 (m, 3H); 2.00 (m, 1H); 2.07 (s, 3H); 2.30-2.50 (m, 3H); 2.54 (m,  
 20 1H); 2.69 (m, 1H); 2.79 (m, 1H); 2.88 (m, 1H); 3.45 (m, 2H); 3.60 (m, 4H); 7.25 (m, 2H); 7.31 (m, 3H).

To a mixture of **134** (0.358 g; 1.25 mmol) in methanol (3 ml) were added ammonium formate (0.236 g; 3.74 mmol) and Pd/C (0.013 g, 0.125 mmol). The reaction was heated at reflux for  
 25 one hour, then filtered through celite. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 10-20% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give **135** as an oil.

Yield: 66%

MS-ESI: 198 [M+H]<sup>+</sup>

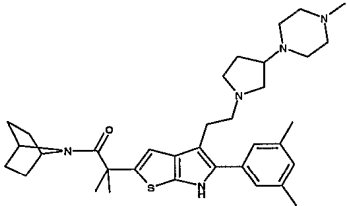
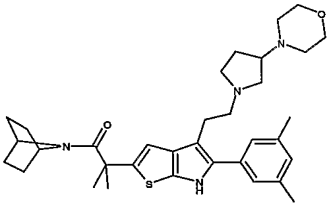
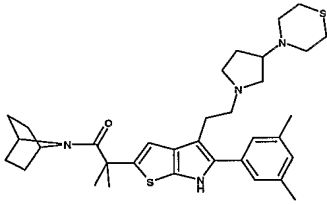
**- 179 -**

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.65 (m, 1H); 1.97 (m, 1H); 2.08 (s, 3H); 2.08 (br m, 2H); 2.41-2.50 (m, 3H); 2.76 (m, 2H); 2.97 (m, 1H); 3.07 (m, 1H); 3.12 (m, 1H); 3.47 (m, 2H); 3.62 (m, 2H).

**Examples 49.1 –49.3**

- 5 Following a procedure similar to that described in **Example 49**, the compounds of **table 49** were prepared.

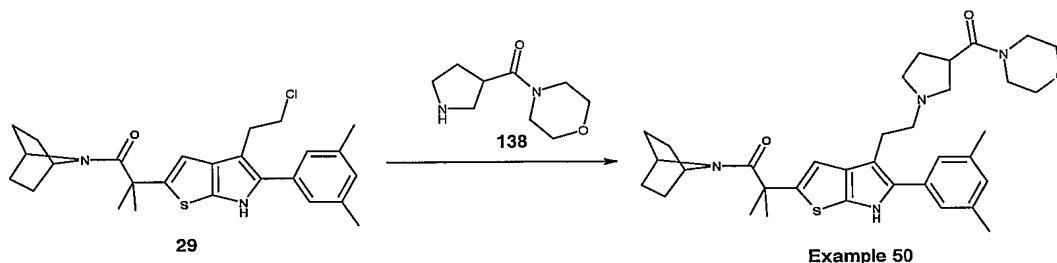
**Table 49**

Example		MS-ESI
<b>49.1</b>		588 $[\text{M}+\text{H}]^+$
<b>49.2</b>		575 $[\text{M}+\text{H}]^+$
<b>49.3</b>		591 $[\text{M}+\text{H}]^+$

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**Example 50**

**2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-4-[2-(3-{morpholinocarbonyl}pyrrolidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole**



5

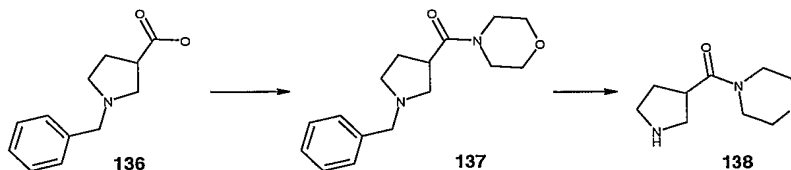
A mixture of **29** (0.139 g; 0.31 mmol), **138** (0.062 g; 0.34 mmol), NaI (0.046 g; 0.31 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.051 g; 0.37 mmol) in dimethylacetamide (3 ml) was heated at 85°C under argon atmosphere for 3 hours. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 1-3% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give after trituration in ether/pentane **Example 50** as a white solid.

Yield: 62%

MS-ESI: 603 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.31 (m, 4H); 1.45-1.80 (m, 4H); 1.62 (s, 6H); 2.05-2.15 (m, 2H); 2.35 (s, 6H); 2.49 (m, 1H); 2.65 (m, 1H); 2.75 (m, 1H); 2.82 (m, 1H); 2.96 (m, 3H); 3.04 (m, 1H); 3.19 (m, 1H); 3.48 (m, 2H); 3.65 (m, 6H); 4.10 (br m, 1H); 4.75 (br m, 1H); 6.74 (s, 1H); 6.94 (s, 1H); 7.06 (s, 2H); 8.13 (s, 1H).

**138** was prepared as follows :



A mixture of **136** (0.127 g; 0.62 mmol), morpholine (0.081 ml; 0.93 mmol), EDCI (0.143 g; 0.74 mmol) and HOBT (0.084 g; 0.62 mmol) in methylene chloride (5 ml) was stirred at room temperature under argon atmosphere for 24 hours. The crude mixture was dissolved in ethyl acetate and washed with a 2 N NaOH solution. The organic layer was dried on magnesium sulphate, evaporated and purified by flash chromatography eluting with a gradient 5-10% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give **137** as an oil.

Yield: 75%

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MS-ESI: 275  $[M+H]^+$ 

$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 2.00-2.15 (m, 2H); 2.46 (q,  $J = 9$  Hz, 1H); 2.60 (t,  $J = 8.5$  Hz, 1H); 2.83 (m, 1H); 2.94 (t,  $J = 9$  Hz, 1H); 3.16 (m, 1H); 3.47 (m, 2H); 3.65 (m, 8H); 7.24 (m, 2H); 7.32 (m, 3H).

5

To a mixture of **137** (0.108 g; 0.30 mmol) in methanol (5 ml) were added ammonium formate (0.074 g; 1.18 mmol) and Pd/C (0.004 g; 0.04 mmol). The reaction was heated at reflux for 3 hours, then filtered through celite. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 20-22% of 3.5 N  $\text{NH}_3$  in MeOH / methylene chloride

10 to give **138** as an oil.

Yield: 88%

MS-ESI: 185  $[M+H]^+$ 

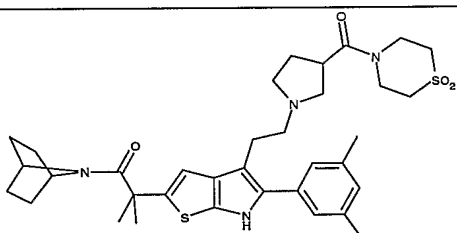
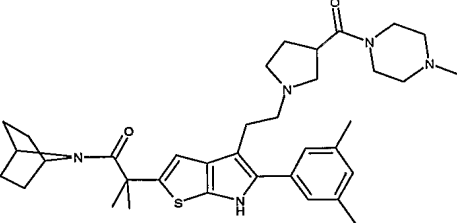
$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 2.07 (m, 2H); 3.01 (m, 1H); 3.07 (m, 1H); 3.16 (m, 2H); 3.28 (m, 1H); 3.53 (m, 2H); 3.62 (m, 2H); 3.67 (m, 5H).

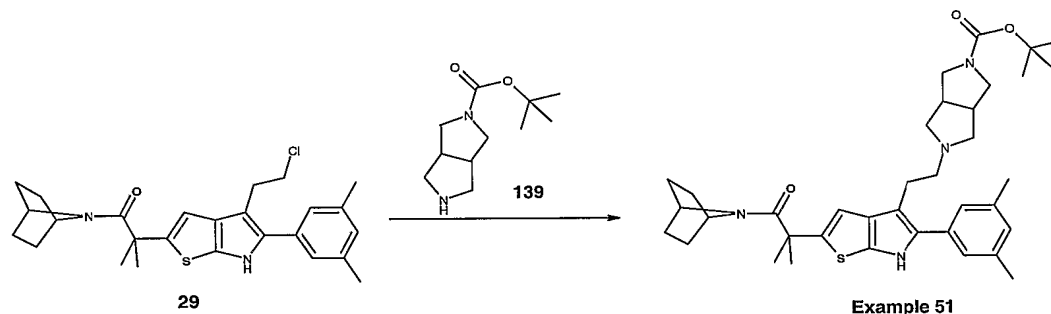
15

**Examples 50.1 –50.3**

Following a procedure similar to that described in **Example 50**, the compounds of **table 50** were prepared.

**Table 50**

Example		MS-ESI
<b>50.1</b>		651 $[M+H]^+$
<b>50.2</b>		616 $[M+H]^+$

**Example 51****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-****4-[2-(5-*t*-butoxycarbonyl-octahydropyrrolo[3,4-c]pyrrol-2-yl)ethyl]-5-(3,5-****5 dimethylphenyl)-6H-thieno[2,3-b]pyrrole**

A mixture of **29** (0.123 g; 0.27 mmol), **139** (0.063 g, 0.30 mmol), NaI (0.040g; 0.27 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.045 g; 0.32 mmol) in dimethylacetamide (3 ml) was heated at 85°C under argon atmosphere for 3 hours. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 1-3% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give after trituration in ether/pentane **Example 51** as a white solid.

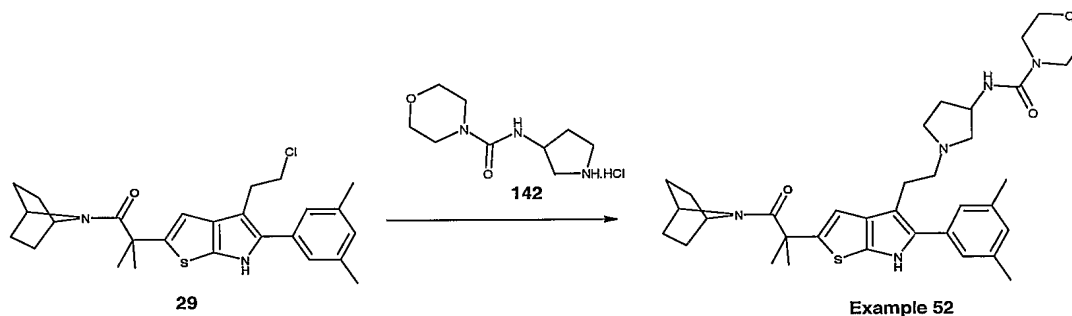
Yield: 78%

MS-ESI: 631 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.31 (m, 6H); 1.45 (s, 9H); 1.50-1.75 (m, 4H); 1.62 (s, 6H); 2.35 (s, 6H); 2.72 (m, 2H); 2.80 (m, 4H); 2.94 (m, 2H); 3.25 (br m, 2H); 3.55 (br m, 2H); 4.10-4.20 (br m, 1H); 4.70-4.80 (br m, 1H); 6.74 (s, 1H); 6.95 (s, 1H); 7.07 (s, 2H); 8.12 (s, 1H).

**Examples 51.1**Example **51.1** was obtained by deprotection of **Example 50** with HCl in dioxane.**Table 51**

Example		MS-ESI
<b>51.1</b>		531 [M+H] <sup>+</sup>

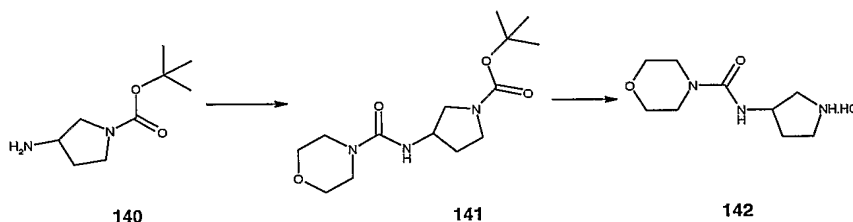
**Example 52****2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-****4-[2-(3-{morpholinocarbonylamino}pyrrolidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6H-****5 thieno[2,3-b]pyrrole**

A mixture of **29** (0.200 g; 0.44 mmol), **142** (0.178 g, 0.76 mmol), NaI (0.066g; 0.44 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.243 g; 1.76 mmol) in dimethylacetamide (4 ml) was heated at 85°C under argon atmosphere for 4 hours. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 2-4% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give after trituration in ether/pentane **Example 52** as a pale brown solid.

Yield: 42%

MS-ESI: 618 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.25-1.40 (m, 4H); 1.62 (s, 6H); 1.50-1.80 (m, 4H); 2.20-2.40 (m, 3H); 2.35 (s, 6H); 2.52 (m, 1H); 2.74 (m, 3H); 2.95 (m, 3H); 3.32 (m, 4H); 3.67 (m, 4H); 4.10 (br m, 1H); 4.39 (br m, 1H); 4.71 (br m, 1H); 4.87 (br m, 1H); 6.74 (s, 1H); 6.95 (s, 1H); 7.06 (s, 2H); 8.16 (s, 1H).

**142** was prepared as follows :

20

To a solution of **140** (0.500 g; 2.68 mmol) in methylene chloride (10 ml) were added at 0°C triethylamine (0.410 ml; 2.95 mmol) then *p*-nitrochloroformate (0.594 g; 2.95 mmol). After 1 hour, morpholine (0.260 ml; 2.95 mmol) was added and the reaction mixture was stirred at room temperature under argon atmosphere for 24 hours. The crude mixture was washed with water. The organic layer was dried on magnesium sulphate, evaporated and purified by flash

25



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chromatography eluting with pure AcOEt first, then with 10% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give **141** as a white foam.

Yield: 86%

MS-ESI: 300 [M+H]<sup>+</sup>

- <sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.46 (s, 9H); 1.75-1.90 (m, 1H); 2.15 (m, 1H); 3.15 (m, 1H); 3.34 (m, 4H); 3.30-3.50 (m, 2H); 3.65 (m, 1H); 3.69 (m, 4H); 4.30-4.50 (m, 2H).

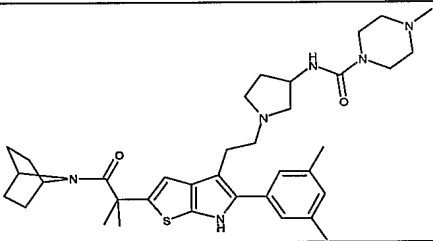
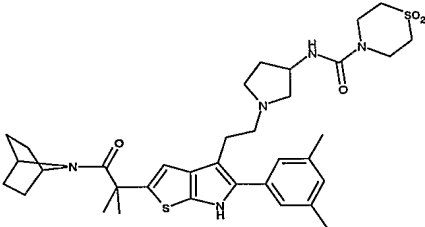
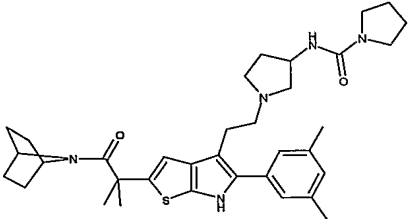
To a solution of **141** (0.680 g; 2.27 mmol) in dioxane (22 ml) was added concentrated HCl (0.60 ml). The reaction was stirred at room temperature for 7 hours, then evaporated to give after trituration in methylene chloride/ether/pentane **142** as a pale brown foam, which was used without further characterisation in **Example 52**.

Yield: 47%

**Examples 52.1 –52.3**

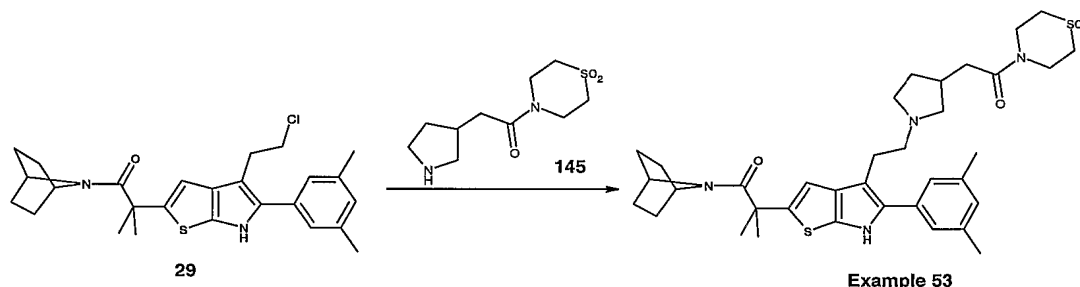
- Following a procedure similar to that described in **Example 52**, the compounds of **table 52** were prepared.

**Table 52**

Example		MS-ESI
<b>52.1</b>		631 [M+H] <sup>+</sup>
<b>52.2</b>		666 [M+H] <sup>+</sup>
<b>52.3</b>		602 [M+H] <sup>+</sup>

**Example 53**

2-[1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl]-  
4-[2-(3-{1,1-dioxothiomorpholin-4-ylcarbonylmethyl}pyrrolidin-1-yl)ethyl]-5-(3,5-  
5 dimethylphenyl)-6H-thieno[2,3-b]pyrrole



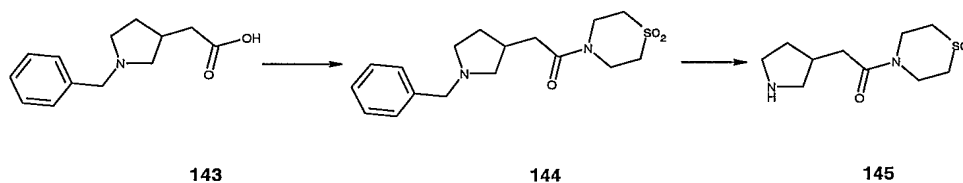
A mixture of **29** (0.250 g; 0.55 mmol), **145** (0.203 g, 0.83 mmol), NaI (0.082 g; 0.55 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.228 g; 1.65 mmol) in dimethylacetamide (3 ml) was heated at 85°C under argon atmosphere for 4 hours. The crude mixture was evaporated and purified by flash chromatography eluting with a gradient 2-6% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give after trituration in ether/pentane **Example 53** as a solid.

Yield: 62%

MS-ESI: 665 [M+H]<sup>+</sup>

<sup>1</sup>H NMR (CDCl<sub>3</sub>) : 1.32 (m, 4H); 1.62 (s, 6H); 1.40-1.78 (m, 8H); 2.16 (s, 1H); 2.35 (s, 6H);  
15 2.52 (m, 3H); 2.65-2.78 (m, 4H); 2.95 (m, 2H); 3.02 (m, 3H); 3.95 (m, 2H); 4.10 (br m, 3H);  
4.72 (br m, 1H); 6.73 (s, 1H); 6.95 (s, 1H); 7.07 (s, 2H); 8.16 (s, 1H).

**145** was prepared as follows :



A mixture of **143** (0.558 g; 2.54 mmol), thiomorpholine-1,1-dioxide (0.516 g; 3.82 mmol), EDCI (0.585 g; 3.05 mmol) and HOBT (0.344 g; 2.54 mmol) in methylene chloride (10 ml) was stirred at room temperature under argon atmosphere for 24 hours. The crude mixture was dissolved in ethyl acetate and washed with a 2 N NaOH solution. The organic layer was dried on magnesium sulphate, evaporated and purified by flash chromatography eluting with a  
25 gradient 5-10% of 3.5 N NH<sub>3</sub> in MeOH / methylene chloride to give **144** as an oil.

Yield: 82%

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$^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.43 (m, 1H); 2.13 (m, 1H); 2.27 (m, 1H); 2.48 (m, 3H); 2.66 (m, 3H); 2.99 (m, 4H); 3.54 (d,  $J = 13$  Hz, 1H); 3.62 (d,  $J = 13$  Hz, 1H); 3.92 (m, 2H); 4.07 (m, 2H); 7.26 (m, 2H); 7.30 (m, 3H).

- 5 To a mixture of **144** (0.698 g; 2.08 mmol) in methanol (10 ml) were added ammonium formate (0.432 g; 6.85 mmol) and Pd/C (0.022 g; 0.21 mmol). The reaction was heated at reflux for 1.5 hours, then filtered through celite. The crude mixture was evaporated to give **145** as an oil used without further purification.

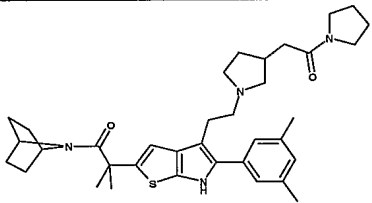
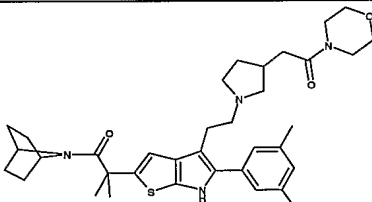
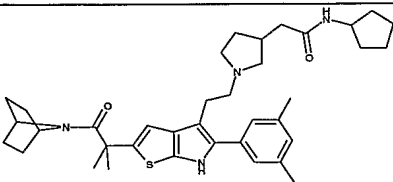
Yield: 95%

- 10  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 1.73 (m, 1H); 2.25 (m, 2H); 2.55 (m, 1H); 2.70 (m, 1H); 2.85 (m, 1H); 3.03 (m, 4H); 3.19 (m, 2H); 3.38 (m, 2H); 3.87-4.07 (m, 3H); 4.24 (m, 1H).

**Examples 53.1 –53.3**

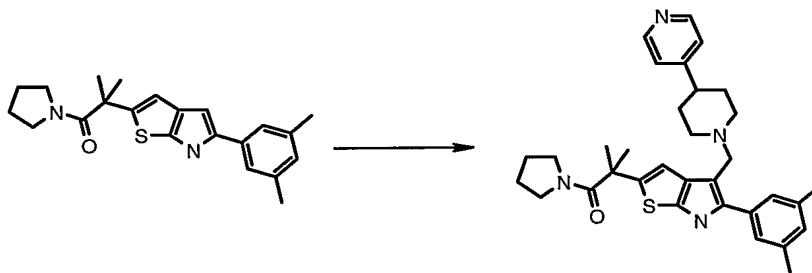
- Following a procedure similar to that described in **Example 53**, the compounds of **table 53**  
15 were prepared.

**Table 53**

Example		MS-ESI
<b>53.1</b>		601 $[\text{M}+\text{H}]^+$
<b>53.2</b>		617 $[\text{M}+\text{H}]^+$
<b>53.3</b>		615 $[\text{M}+\text{H}]^+$

**Example 54**

**2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-4-[(4-pyridin-4-yl)piperidin-1-yl)methyl]-6H-thieno[2,3-*b*]pyrrole**



Example 54

5 4-piperidin-4-ylpyridine (see: Brown, George Robert; Newcombe, Nicholas John; Foubister, Alan John. 1-(Arylsulfonyl)-4-[[4-(4-pyridyl)piperidin-1-yl]carbonyl]piperazines and analogs useful as oxido-squalene cyclase inhibitors. PCT Int. Appl. (1998), WO 9835959 A1 19980820 CAN 129:189345 AN 1998:568822) (0.033g, 0.20mmol) was added to a solution of formaldehyde in acetic acid (2.8ml made up from 0.61ml of a 37% formaldehyde aqueous solution in 100ml of acetic acid, 0.21mmol) and the mixture was stirred at ambient temperature for five minutes. A solution of 2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-6H-thieno[2,3-*b*]pyrrole as a 1.1 : 1 mixture with triethyl phosphite (0.083g, 0.16mmol) in acetic acid (1ml) was added dropwise and the mixture was then allowed to stir at ambient temperature for 30 minutes. The mixture was concentrated under vacuum and the residue partitioned between 2N hydrochloric acid and ethyl acetate. The aqueous layer was separated, made basic by the addition of 2N sodium hydroxide and extracted with ethyl acetate. The organic layer was separated, washed with a saturated brine solution, dried over magnesium sulfate and then evaporated to leave a yellow oil. Flash chromatography on silica eluting with 2 – 3% methanol (containing 7N ammonia) in dichloromethane gave the product as a pale yellow solid (0.043g).

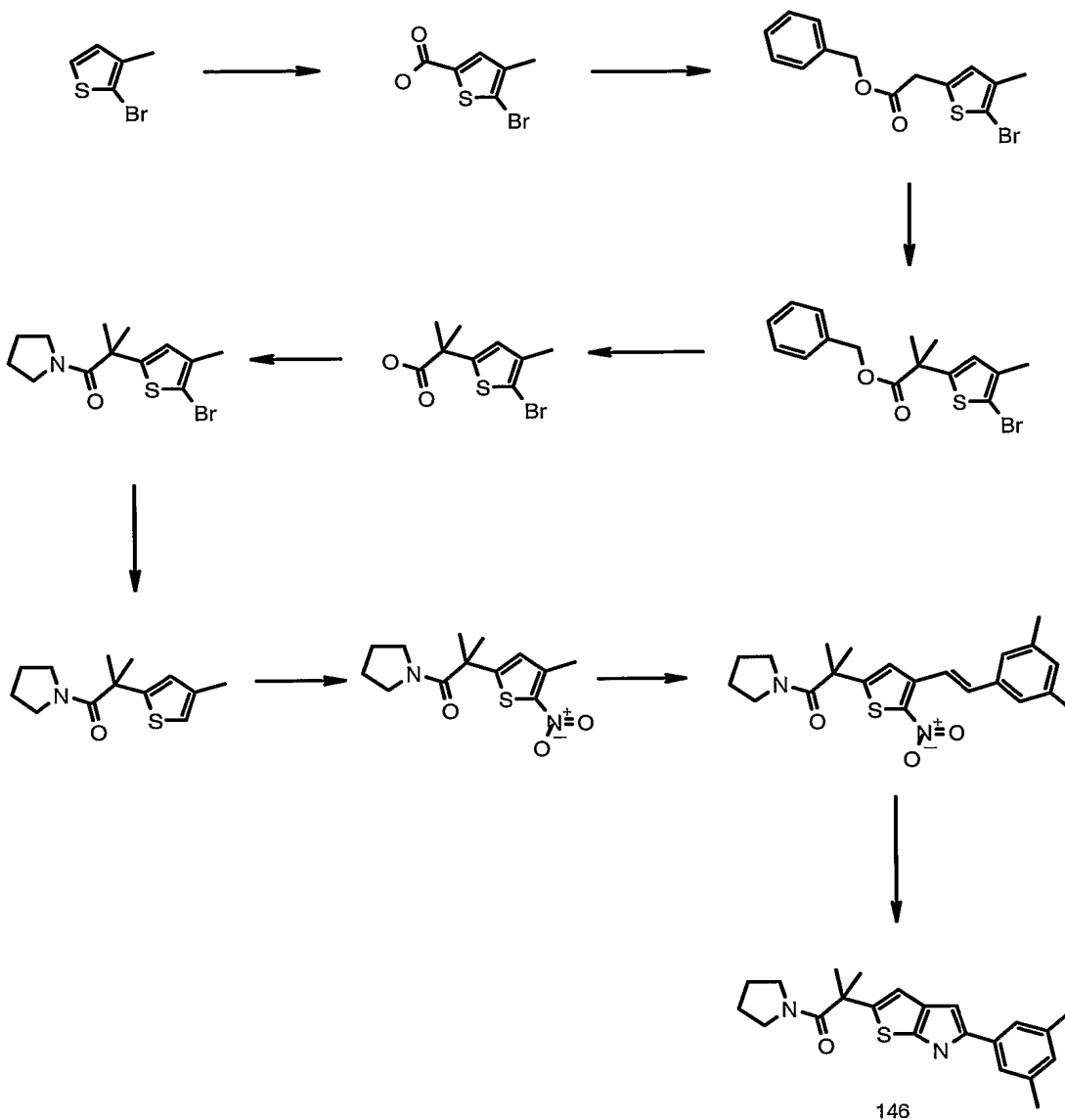
Yield: 50 %

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.6-1.76 (m, 12H + H<sub>2</sub>O), 1.78-1.86 (m, 2H), 2.10-2.18 (m, 2H), 2.36 (s, 6H), 2.46-2.55 (m, 1H), 3.08-3.20 (m, 4H), 3.50-3.58 (m, 2H), 3.60 (s, 2H), 6.84 (s, 1H), 6.95 (s, 1H), 7.14 (d, 2H), 7.28 (s, 2H), 8.45 (s, 1H), 8.50 (d, 2H).

25 MS-ESI: 541 [M+H]<sup>+</sup>

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Intermediate **146** was prepared according to the following scheme:



2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-  
5 *b*]pyrrole was prepared as follows:  
5-Bromo-4-methylthiophene-2-carboxylic acid (Nemec, M.; Janda, Miroslav; Srogl, Jan;  
Stibor, I. Collection of Czechoslovak Chemical Communications (1974), 39(12), 3527-31.)  
(2.5g, 11mmol) was suspended in dichloromethane (25ml) and dimethylformamide (0.1ml).  
Oxalyl chloride (1.1ml, 13mmol) was added and the mixture was allowed to stir at ambient  
10 temperature for 2 hours. The solvent was evaporated and the crude acid chloride was dried  
under vacuum. The acid chloride was dissolved in a mixture of acetonitrile (20ml),  
tetrahydrofuran (20ml) and triethylamine (2.0ml, 14mmol) and the mixture was cooled in an

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ice-bath. A solution of (trimethylsilyl)diazomethane (8.5ml) in hexane (2.0M, 17mmol) was added dropwise and the mixture allowed to stir in an ice-bath for 20 hours. The solvent was evaporated and the residue partitioned between 1N hydrochloric acid and ethyl acetate. The organic layer was separated, dried over magnesium sulfate and then evaporated to leave a yellow solid. The crude *alpha*-diazoketone was dissolved in a mixture of benzyl alcohol (10ml) and 2,4,6-trimethylpyridine (10ml) and heated to 180 C for 2 hours. The mixture was allowed to cool and then purified directly by flash chromatography on silica eluting with a mixture of 10% ethyl acetate in *iso*-hexane to afford benzyl (5-bromo-4-methyl-2-thienyl)acetate (0.982g) as a dark yellow oil

10 Yield: 27%

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 2.12 (s, 3H), 3.74 (s, 2H), 5.15 (s, 2H), 6.61 (s, 1H), 7.32-7.37 (m, 5H).

MS-ESI: 325 / 327 [M+H]<sup>+</sup>

A solution of benzyl (5-bromo-4-methyl-2-thienyl)acetate (0.982g, 3.02mmol) in tetrahydrofuran (3.5ml) was added dropwise to a solution of lithium di-*iso*-propyl amide [made from di-*iso*-propyl amine (1.02ml, 7.3mmol) and a solution of *n*-butyl lithium (4.54ml) in hexane (1.6M, 7.26mmol) in tetrahydrofuran (5ml)] cooled to -78 C. The mixture was stirred for 2 hours at -78 C and then methyl iodide (1.0ml, 16mmol) was added and the mixture was allowed to warm to ambient temperature over 4 hours. The mixture was poured into water and extracted with ethyl acetate. The organic layer was separated and then washed with a 1N solution of hydrochloric acid followed by a saturated solution of brine. The ethyl acetate solution was dried over magnesium sulfate and then evaporated to leave benzyl 2-(5-bromo-4-methyl-2-thienyl)-2-methylpropanoate as a yellow oil which was used in the next step without further purification.

25 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.61 (s, 6H), 2.11 (s, 3H), 5.12 (s, 2H), 6.59 (s, 1H), 7.25-7.37 (m, 5H).

A mixture of the benzyl 2-(5-bromo-4-methyl-2-thienyl)-2-methylpropanoate and sodium hydroxide (0.33g, 8.3mmol) in methanol (10ml) and water (2.5ml) was heated under reflux for 1hour. The solvent was evaporated and the residue triturated with 1N hydrochloric acid and then extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate and then evaporated to leave 2-(5-bromo-4-methyl-2-thienyl)-2-methylpropanoic acid as a yellow gum which was used in the next step without purification.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 2.09 (s, 6H), 2.13 (s, 3H), 6.69 (s, 1H).

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To a mixture of the 2-(5-bromo-4-methyl-2-thienyl)-2-methylpropanoic acid in dichloromethane (10ml) with a catalytic amount of dimethylformamide was added oxalyl chloride (0.30ml, 0.34mmol). The mixture was allowed to stir at ambient temperature for 2 hours. The solvent was evaporated and the crude acid chloride dried under vacuum. The crude acid chloride was dissolved in dichloromethane (10ml) and cooled in an ice-bath. Pyrrolidine (1.2ml, 14mmol) was added and the mixture was allowed to stir for 30 minutes while being cooled in an ice-bath. The mixture was poured into ethyl acetate (25ml) and then extracted with 1N hydrochloric acid. The organic layer was washed with a saturated brine solution, dried over magnesium sulfate and then evaporated to leave 1-[2-(5-bromo-4-methyl-2-thienyl)-2-methylpropanoyl]pyrrolidine as a red oil which was used in the next step without purification.

MS-ESI: 316 / 318 [M+H]<sup>+</sup>

To a solution of the 1-[2-(5-bromo-4-methyl-2-thienyl)-2-methylpropanoyl]pyrrolidine in acetic acid (8ml) and water (5ml) was added zinc dust (1.0g, 15mmol). The mixture was heated under reflux for 24 hours. The solvent was evaporated and the residue was dissolved in ethyl acetate and then washed sequentially with 1N hydrochloric acid, 1N sodium hydroxide and a saturated brine solution. The ethyl acetate solution was dried over magnesium sulfate and then evaporated. The residue was purified by flash chromatography on silica eluting with a 20-75% mixture of ethyl acetate in *iso*-hexane to afford 1-[2-methyl-2-(4-methyl-2-thienyl)propanoyl]pyrrolidine (0.151g) as a colourless solid.

Yield: 21% over 4 steps from benzyl (5-bromo-4-methyl-2-thienyl)acetate.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.46 (s, 6H), 1.56-1.65 (m, 4H), 2.14 (s, 3H), 2.90 (br, 2H), 3.30 (br, 2H), 6.67 (d, 1H), 6.92-6.95 (m, 1H).

MS-ESI: 238 [M+H]<sup>+</sup>

Nitronium tetrafluoroborate (0.168g, 1.26mmol) was added to a solution of 1-[2-methyl-2-(4-methyl-2-thienyl)propanoyl]pyrrolidine (0.145g, 0.61mmol) in dimethoxy ethane (5ml) cooled to -50°C. The mixture was allowed to warm to -30°C over 1 hour. The mixture was poured into water and extracted with ethyl acetate. The organic layer was separated and washed sequentially with a saturated solution of sodium bicarbonate and then with a saturated

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brine solution. The ethyl acetate solution was dried over magnesium sulfate and then evaporated to afford 1-[2-methyl-2-(4-methyl-5-nitro-2-thienyl)propanoyl]pyrrolidine as a yellow solid which was used in the next step without purification.

<sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.62 (s, 6H), 1.73-1.81 (m, 4H), 2.58 (s, 3H), 3.03 (br, 2H), 3.53 (br, 2H),  
5 6.66 (3, 1H).

A mixture of the 1-[2-methyl-2-(4-methyl-5-nitro-2-thienyl)propanoyl]pyrrolidine and 3,5-dimethylbenzaldehyde (0.161g, 1.2mmol) in ethanol (5ml) containing a catalytic amount of pyrrolidine was heated under reflux for 18 hours. The mixture was allowed to cool to ambient  
10 temperature and then the precipitate was filtered. The solid was washed with cold ethanol (2x 5ml) and then dried under vacuum to leave 1-(2-{4-[(*E*)-2-(3,5-dimethylphenyl)vinyl]-5-nitro-2-thienyl}-2-methylpropanoyl pyrrolidine (0.144g) as a bright yellow fluffy solid which was used in the next step without further purification.

Yield: 59% over two steps from 1-[2-methyl-2-(4-methyl-2-thienyl)propanoyl] pyrrolidine.  
15 <sup>1</sup>H NMR (d<sub>6</sub> DMSO): 1.57 (s, 6H), 1.64-1.70 (m, 4H), 2.30 (s, 6H), 3.04 (br, 2H), 3.37 (br, 2H), 7.02 (s, 1H), 7.25 (s, 2H), 7.61 (s, 1H), 7.63 (d, 1H), 7.88 (d, 1H).

A mixture 1-(2-{4-[(*E*)-2-(3,5-dimethylphenyl)vinyl]-5-nitro-2-thienyl}-2-methylpropanoyl pyrrolidine (0.140g, 0.35mmol) and triethyl phosphite (1.0ml) was heated at 180 C for 1 hour.  
20 The mixture was concentrated and the residue purified directly by flash chromatography on silica eluting with a mixture of 20% ethyl acetate in *iso*-hexane to afford 2-(1,1-dimethyl-2-oxo-2-pyrrolidin-1-ylethyl)-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole (0.107g) as a red oil which was a 1.1 : 1 mixture with triethyl phosphite.

Yield: 59% (based on 1.1 : 1 mixture with triethyl phosphite)  
25 <sup>1</sup>H NMR (CDCl<sub>3</sub>): 1.65 (s, 6H), 1.70 (br, 4H), 2.34 (s, 6H), 3.13 (br, 2H), 3.54 (br, 2H), 6.57 (d, 1H), 6.74 (s, 1H), 6.87 (s, 1H), 7.19 (s, 2H), 9.25 (s, 1H).

MS-ESI: 367 [M+H]<sup>+</sup>

### THERAPEUTIC USES

30 Compounds of Formula (I) are provided as medicaments for antagonising gonadotropin releasing hormone (GnRH) activity in a patient, eg, in men and/or women. To this end, a compound of Formula (I) can be provided as part of a pharmaceutical formulation which also includes a pharmaceutically acceptable diluent or carrier (eg, water). The



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formulation may be in the form of tablets, capsules, granules, powders, syrups, emulsions (eg, lipid emulsions), suppositories, ointments, creams, drops, suspensions (eg, aqueous or oily suspensions) or solutions (eg, aqueous or oily solutions). If desired, the formulation may include one or more additional substances independently selected from stabilising agents, wetting agents, emulsifying agents, buffers, lactose, sialic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter and ethylene glycol.

The compound is preferably orally administered to a patient, but other routes of administration are possible, such as parenteral or rectal administration. For intravenous, subcutaneous or intramuscular administration, the patient may receive a daily dose of  $0.1\text{mgkg}^{-1}$  to  $30\text{mgkg}^{-1}$  (preferably,  $5\text{mgkg}^{-1}$  to  $20\text{mgkg}^{-1}$ ) of the compound, the compound being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively, the intravenous dose may be given by continuous infusion over a period of time. Alternatively, the patient may receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day. A suitable pharmaceutical formulation is one suitable for oral administration in unit dosage form, for example as a tablet or capsule, which contains between 10mg and 1g (preferably, 100 mg and 1g) of the compound of the invention.

Buffers, pharmaceutically acceptable co-solvents (eg, polyethylene glycol, propylene glycol, glycerol or EtOH) or complexing agents such as hydroxy-propyl  $\beta$  cyclodextrin may be used to aid formulation.

One aspect of the invention relates to the use of compounds according to the invention for reducing the secretion of LH and/or FSH by the pituitary gland of a patient. In this respect, the reduction may be by way of a reduction in biosynthesis of the LH and FSH and/or a reduction in the release of LH and FSH by the pituitary gland. Thus, compounds according to the invention can be used for therapeutically treating and/or preventing a sex hormone related condition in the patient. By "preventing" we mean reducing the patient's risk of contracting the condition. By "treating" we mean eradicating the condition or reducing its severity in the patient. Examples of sex hormone related conditions are: a sex hormone dependent cancer, benign prostatic hypertrophy, myoma of the uterus, endometriosis, polycystic ovarian disease, uterine fibroids, prostataux, myoma uteri, hirsutism and precocious puberty. Examples of sex hormone dependent cancers are: prostatic cancer,

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uterine cancer, breast cancer and pituitary gonadotrophe adenoma.

The compounds of the invention may be used in combination with other drugs and therapies used to treat / prevent sex-hormone related conditions.

If formulated as a fixed dose such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically-active agent within its approved dosage range. Sequential use is contemplated when a combination formulation is inappropriate.

In the field of medical oncology examples of such combinations include combinations with the following categories of therapeutic agent:

- 10 i) anti-angiogenic agents (for example linomide, inhibitors of integrin  $\alpha v \beta 3$  function, angiostatin, endostatin, razoxin, thalidomide) and including vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitors (RTKIs) (for example those described in international patent applications publication nos. WO-97/22596, WO-97/30035, WO-97/32856 and WO-98/13354, the entire disclosure of which documents is incorporated  
15 herein by reference);
- ii) cytostatic agents such as anti-oestrogens (for example tamoxifen, toremifene, raloxifene, droloxifene, idoxifene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrozole, vorazole, exemestane), anti-progestogens, anti-androgens (for example flutamide, nilutamide, bicalutamide, cyproterone  
20 acetate), inhibitors of testosterone  $5\alpha$ -dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example epidermal growth factor (EGF), platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies,  
25 growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors);
- iii) biological response modifiers (for example interferon);
- iv) antibodies (for example edrecolomab); and
- v) anti-proliferative/anti-neoplastic drugs and combinations thereof, as used  
30 in medical oncology, such as anti-metabolites (for example anti-folates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); anti-tumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example

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cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); anti-mitotic agents (for example vinca alkaloids like vincristine and taxoids like taxol, taxotere); enzymes (for example asparaginase); thymidylate synthase inhibitors (for example raltitrexed);

5 topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan, irinotecan).

The compounds of the invention may also be used in combination with surgery or radiotherapy.

## 10 ASSAYS

The ability of compounds according to the invention to act as antagonists of GnRH can be determined using the following in vitro assays.

### Binding Assay Using Rat pituitary GnRH Receptor

The assay is performed as follows:-

- 15 1. Incubate crude plasma membranes prepared from rat pituitary tissues in a Tris.HCl buffer (pH. 7.5, 50 mM) containing bovine serum albumin (0.1%), [I-125]D-t-Bu-Ser6-Pro9-ethyl amide-GnRH, and the test compound. Incubation is at 4<sup>0</sup>C for 90 minutes to 2 hours.
2. Rapidly filter and repeatedly wash through a glass fibre filter.
- 20 3. Determine the radioactivity of membrane bound radio-ligands using a gamma counter.

From this data, the IC<sub>50</sub> of the test compound can be determined as the concentration of the compound required to inhibit radio-ligand binding to GnRH receptors by 50%.

Compounds according to the present invention have activity at a concentration from 1nM to 5 μM.

25

### Binding Assay Using Human GnRH Receptor

Crude membranes prepared from CHO cells expressing human GnRH receptors are sources for the GnRH receptor. The binding activity of compounds according to the invention can be determined as an IC<sub>50</sub> which is the compound concentration required to inhibit the

- 30 specific binding of [<sup>125</sup>I]buserelin to GnRH receptors by 50%. [<sup>125</sup>I]Buserelin (a peptide GnRH analogue) is used here as a radiolabelled ligand of the receptor.

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Assay to Determine Inhibition of LH release

The LH release assay can be used to demonstrate antagonist activity of compounds, as demonstrated by a reduction in GnRH-induced LH release.

5 Preparation of Pituitary Glands

Pituitary glands obtained from rats are prepared as follows. Suitable rats are Wistar male rats (150-200g) which have been maintained at a constant temperature (eg, 25°C) on a 12 hour light/12 hour dark cycle. The rats are sacrificed by decapitation before the pituitary glands are aseptically removed to tube containing Hank's Balanced Salt Solution (HBSS).

10 The glands are further processed by:-

1. Centrifugation at 250 x g for 5 minutes;
2. Aspiration of the HBSS solution;
3. Transfer of the glands to a petri dish before mincing with a scalpel;
- 15 4. Transfer of the minced tissue to a centrifuge tube by suspending the tissue three successive times in 10 ml aliquots of HBSS containing 0.2% collagenase and 0.2% hyaluronidase;
5. Cell dispersion by gentle stirring of the tissue suspension while the tube is kept in a water bath at 37°C;
- 20 6. Aspiration 20 to 30 times using a pipette, undigested pituitary fragments being allowed to settle for 3 to 5 minutes;
7. Aspiration of the suspended cells followed by centrifugation at 1200 x g for 5 minutes;
8. Re-suspension of the cells in culture medium of DMEM containing 0.37% NaHCO<sub>3</sub>, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids, 1% glutamine and
- 25 0.1% gentamycin;
9. Treatment of the undigested pituitary fragments 3 times with 30 ml aliquots of the collagenase and hyaluronidase;
10. Pooling of the cell suspensions and dilution to a concentration of  $3 \times 10^5$  cells/ml;
11. Placing of 1.0ml of this suspension in each of a 24 well tray, with the cells being
- 30 maintained in a humidified 5% CO<sub>2</sub>/95% air atmosphere at 37°C for 3 to 4 days

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### Testing of Compounds

The test compound is dissolved in DMSO to a final concentration of 0.5% in the incubation medium.

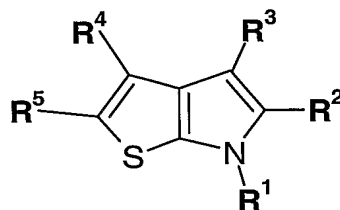
1.5 hours prior to the assay, the cells are washed three times with DMEM containing  
5 0.37% NaHCO<sub>3</sub>, 10% horse serum, 2.5% foetal bovine serum, 1% non essential amino acids (100X), 1% glutamine (100X), 1% penicillin/streptomycin (10,000 units of each per ml) and 25 mM HEPES at pH 7.4. Immediately prior to the assay, the cells are again washed twice in this medium .

Following this, 1ml of fresh medium containing the test compound and 2nM GnRH is  
10 added to two wells. For other test compounds (where it is desired to test more than one compound), these are added to other respective duplicate wells. Incubation is then carried out at 37°C for three hours.

Following incubation, each well is analysed by removing the medium from the well and centrifuging the medium at 2000 x g for 15 minutes to remove any cellular material. The  
15 supernatant is removed and assayed for LH content using a double antibody radio-immuno assay. Comparison with a suitable control (no test compound) is used to determine whether the test compound reduces LH release. Compounds according to the present invention have activity at a concentration from 1nM to 5 µM.

**CLAIMS:**

1. A compound of Formula (I),



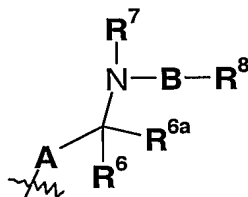
Formula (I)

wherein

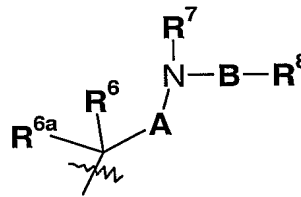
**R¹** is selected from: hydrogen, optionally-substituted C<sub>1-6</sub>alkyl, optionally substituted C<sub>1-6</sub>alkanoyl, optionally substituted aryl or optionally-substituted arylC<sub>1-6</sub>alkyl;

**R²** is an optionally-substituted mono or bi-cyclic aromatic ring;

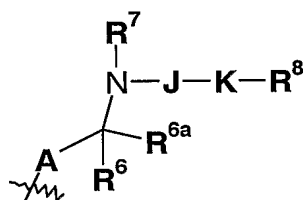
**R³** is selected from a group of Formula (IIa) to Formula (IIf):



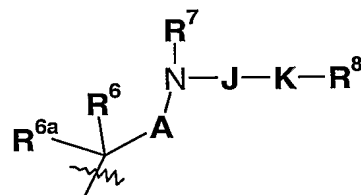
Formula (IIa)



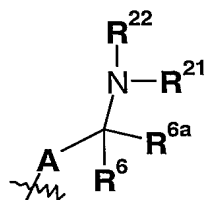
Formula (IIb)



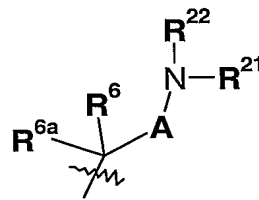
Formula (IIc)



Formula (IId)



Formula (IIe)

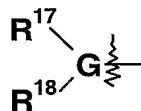


Formula (IIf)

**R⁴** is selected from: hydrogen, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted aryl, C<sub>1-3</sub>perfluoroalkyl, cyano, nitro, halo, **R⁹**O(CH<sub>2</sub>)<sub>m</sub>-, **R⁹**C(O)N(**R¹⁰**)-, **R⁹R¹⁰**NC(O)N(**R¹⁰**)(CH<sub>2</sub>)<sub>m</sub>-, **R⁹**S(O<sub>n</sub>)(CH<sub>2</sub>)<sub>m</sub>- or **R⁹R¹⁰**NC(O)-(CR<sup>9</sup>R<sup>10</sup>)<sub>t</sub>(CH<sub>2</sub>)<sub>m</sub>-;

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**R**<sup>5</sup> is a group of Formula (III):



Formula (III)

**R**<sup>6</sup> and **R**<sup>6a</sup> are independently selected from hydrogen, fluoro, optionally substituted C<sub>1-6</sub>alkyl, optionally-substituted aryl or optionally substituted arylC<sub>1-6</sub>alkyl, or **R**<sup>6</sup> and **R**<sup>6a</sup> taken together and the carbon atom to which they are attached form a carbocyclic ring of 3-7 atoms, or **R**<sup>6</sup> and **R**<sup>6a</sup> taken together and the carbon atom to which they are attached form a carbonyl group;

or when **A** is not a direct bond the group forms a carbocyclic ring of 3-7 carbon atoms or a heterocyclic ring containing one or more heteroatoms;

or the group forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

**R**<sup>7</sup> is selected from: hydrogen, optionally-substituted C<sub>1-6</sub>alkyl, optionally-substituted arylC<sub>1-6</sub>alkyl, optionally-substituted aryl, optionally substituted heterocyclyl, optionally substituted heterocyclylC<sub>1-6</sub>alkyl, **R**<sup>9</sup>OC<sub>1-6</sub>alkyl-, **R**<sup>9</sup>**R**<sup>10</sup>NC<sub>1-6</sub>alkyl-, **R**<sup>9</sup>**R**<sup>10</sup>NC(O)C<sub>1-6</sub>alkyl, -C(NR<sup>9</sup>R<sup>10</sup>)=NH;

or when **R**<sup>3</sup> is a group of Formula (IIc) or (IId) **R**<sup>7</sup> is of the formula -**J-K-R**<sup>8</sup>;

**R**<sup>8</sup> is selected from:

- (i) hydrogen, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, haloC<sub>1-6</sub>alkyl, C<sub>1-4</sub>alkoxyC<sub>1-4</sub>alkyl, hydroxy, hydroxyC<sub>1-6</sub>alkyl, cyano, N-C<sub>1-4</sub>alkylamino, N,N-di-C<sub>1-4</sub>alkylamino, C<sub>1-6</sub>alkyl-S(O<sub>n</sub>)-, -O-**R**<sup>b</sup>, -NR<sup>b</sup>R<sup>c</sup>, -C(O)-**R**<sup>b</sup>, -C(O)O-**R**<sup>b</sup>, -CONR<sup>b</sup>R<sup>c</sup>, NH-C(O)-**R**<sup>b</sup> or -S(O<sub>n</sub>)NR<sup>b</sup>R<sup>c</sup>, where **R**<sup>b</sup> and **R**<sup>c</sup> are independently selected from hydrogen and C<sub>1-4</sub>alkyl optionally substituted with hydroxy, amino, N-C<sub>1-4</sub>alkylamino, N,N-di-C<sub>1-4</sub>alkylamino, HO-C<sub>2-4</sub>alkyl-NH- or HO-C<sub>2-4</sub>alkyl-N(C<sub>1-4</sub>alkyl)-;

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(ii) nitro when **B** is a group of Formula (IV) and **X** is CH and **p** is 0;

(iii) C<sub>3-7</sub>cycloalkyl, aryl or arylC<sub>1-6</sub>alkyl each of which is optionally substituted by **R**<sup>12</sup>, **R**<sup>13</sup> and **R**<sup>14</sup>;

(iv) -(**Q**)-aryl, -(**Q**)-heterocyclyl, -aryl-(**Q**)-aryl, each of which is optionally substituted by **R**<sup>12</sup>, **R**<sup>13</sup> and **R**<sup>14</sup>

5

wherein -(**Q**)- is selected from **E**, **F** or a direct bond;

(v) heterocyclyl or heterocyclylC<sub>1-6</sub>alkyl each of which is optionally substituted by up to 4 substituents independently selected from **R**<sup>12</sup>, **R**<sup>13</sup> and **R**<sup>14</sup>;

10

(vi) a group selected from **R**<sup>12</sup>, **R**<sup>13</sup> and **R**<sup>14</sup>;

**R**<sup>9</sup> and **R**<sup>10</sup> are independently selected from: hydrogen, hydroxy, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl, an optionally substituted carbocyclic ring of 3-7 atoms, optionally substituted heterocyclyl, optionally substituted heterocyclylC<sub>1-6</sub>alkyl or **R**<sup>9</sup> and **R**<sup>10</sup> taken together can form an optionally substituted ring of 3-9 atoms or **R**<sup>9</sup> and **R**<sup>10</sup> taken together with the carbon atom to which they are attached form a carbonyl group;

15

**R**<sup>11</sup> is selected from: hydrogen, optionally substituted C<sub>1-6</sub>alkyl, or N(**R**<sup>9</sup>**R**<sup>10</sup>);

**R**<sup>12</sup> is selected from: hydrogen, hydroxy, **R**<sup>17</sup>**R**<sup>18</sup>N(CH<sub>2</sub>)<sub>cc</sub>-, **R**<sup>17</sup>**R**<sup>18</sup>NC(O)(CH<sub>2</sub>)<sub>cc</sub>-,

20

optionally substituted C<sub>1-6</sub>alkyl- C(O)N(**R**<sup>9</sup>)(CH<sub>2</sub>)<sub>cc</sub>-, optionally substituted C<sub>1-6</sub>alkyl-SO<sub>2</sub>N(**R**<sup>9</sup>)-, optionally substituted aryl-SO<sub>2</sub>N(**R**<sup>9</sup>)-,

C<sub>1-3</sub>perfluoroalkyl-SO<sub>2</sub>N(**R**<sup>9</sup>)-; optionally substituted C<sub>1-6</sub>alkyl-N(**R**<sup>9</sup>)SO<sub>2</sub>-,

optionally substituted aryl-N(**R**<sup>9</sup>)SO<sub>2</sub>-, C<sub>1-3</sub>perfluoroalkyl-N(**R**<sup>9</sup>)SO<sub>2</sub>- optionally substituted C<sub>1-6</sub>alkanoyl-N(**R**<sup>9</sup>)SO<sub>2</sub>-, optionally substituted aryl-C(O)N(**R**<sup>9</sup>)SO<sub>2</sub>-,

25

optionally substituted C<sub>1-6</sub>alkyl-S(O<sub>n</sub>) -, optionally substituted aryl-S(O<sub>n</sub>) -,

C<sub>1-3</sub>perfluoroalkyl-, C<sub>1-3</sub>perfluoroalkoxy, optionally substituted C<sub>1-6</sub>alkoxy, carboxy, halo, nitro or cyano;

**R**<sup>13</sup> and **R**<sup>14</sup> are independently selected from: hydrogen, hydroxy, oxo, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted C<sub>1-6</sub>alkanoyl, optionally substituted C<sub>2-6</sub>alkenyl, cyano, nitro, C<sub>1-3</sub>perfluoroalkyl-, C<sub>1-3</sub>perfluoroalkoxy, optionally substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl, **R**<sup>9</sup>O(CH<sub>2</sub>)<sub>s</sub>-, **R**<sup>9</sup>(O)O(CH<sub>2</sub>)<sub>s</sub>-, **R**<sup>9</sup>OC(O)(CH<sub>2</sub>)<sub>s</sub>-, **R**<sup>16</sup>S(O<sub>n</sub>)(CH<sub>2</sub>)<sub>s</sub>-, **R**<sup>9</sup>**R**<sup>10</sup>NC(O)(CH<sub>2</sub>)<sub>s</sub>- or halo;

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**R<sup>15</sup>** is selected from: hydrogen, optionally substituted C<sub>1-6</sub>alkyl, **R<sup>19</sup>**OC(O)-, **R<sup>9</sup>R<sup>10</sup>**NC(O)-, **R<sup>9</sup>**C(O)-, **R<sup>9</sup>**S(O<sub>n</sub>)-;

**R<sup>16</sup>** is selected from: hydrogen, C<sub>1-6</sub>alkyl, C<sub>1-3</sub>perfluoroalkyl or optionally-substituted aryl;

5 **R<sup>17</sup>** is independently selected from: hydrogen, hydroxy, cyano or optionally substituted C<sub>1-6</sub>alkyl;

**R<sup>18</sup>** is a group of formula **R<sup>18a</sup>**-C(**R<sup>9</sup>R<sup>10</sup>**)<sub>0-1</sub>- wherein **R<sup>18a</sup>** is selected from:

**R<sup>19</sup>**OC(O)-, **R<sup>9</sup>R<sup>10</sup>**NC(O)-, **R<sup>9</sup>R<sup>10</sup>**N-, **R<sup>9</sup>**C(O)-, **R<sup>9</sup>**C(O)N(**R<sup>10</sup>**)-, **R<sup>9</sup>R<sup>10</sup>**NC(O)-, **R<sup>9</sup>R<sup>10</sup>**NC(O)N(**R<sup>10</sup>**)-, **R<sup>9</sup>**SO<sub>2</sub>N(**R<sup>10</sup>**)-, **R<sup>9</sup>R<sup>10</sup>**NSO<sub>2</sub>N(**R<sup>10</sup>**)-, **R<sup>9</sup>**C(O)O-, **R<sup>9</sup>**OC(O)-,

10 **R<sup>9</sup>R<sup>10</sup>**NC(O)O-, **R<sup>9</sup>**O-, **R<sup>9</sup>**S(O<sub>n</sub>)-, **R<sup>9</sup>R<sup>10</sup>**NS(O<sub>n</sub>)-, hydrogen, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted heterocyclyl;

or **R<sup>17</sup>** and **R<sup>18</sup>** when taken together form an optionally substituted carbocyclic ring of 3-7 atoms or optionally substituted heterocyclyl;

**R<sup>19</sup>** is selected from: hydrogen, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted aryl, optionally substituted arylC<sub>1-6</sub>alkyl, optionally substituted C<sub>3-7</sub>cycloalkyl, optionally substituted heterocyclyl or optionally substituted heterocyclylC<sub>1-6</sub>alkyl;

15

**R<sup>20</sup>** is selected from **R<sup>12</sup>** or **R<sup>13</sup>**;

**R<sup>21</sup>** and **R<sup>22</sup>** are independently selected from hydrogen, optionally substituted C<sub>1-6</sub>alkyl, optionally substituted C<sub>3-7</sub>cycloalkyl, optionally substituted

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heterocyclyl, optionally substituted heterocyclylC<sub>1-6</sub>alkyl, optionally substituted C<sub>3-6</sub>alkenyl, optionally substituted C<sub>3-6</sub>alkynyl, -(C<sub>1-5</sub>alkyl)<sub>aa</sub>-S(O<sub>n</sub>)-(C<sub>1-5</sub>alkyl)<sub>bb</sub>-; **R<sup>9</sup>R<sup>10</sup>**NC<sub>2-6</sub>alkyl, **R<sup>9</sup>**OC<sub>2-6</sub>alkyl or **R<sup>9</sup>R<sup>10</sup>**NC(O)C<sub>2-6</sub>alkyl, with the proviso that **R<sup>9</sup>** and **R<sup>10</sup>** independently or taken together are not optionally substituted aryl or optionally substituted arylC<sub>1-6</sub>alkyl; or

25

**R<sup>21</sup>** and **R<sup>22</sup>** taken together form an optionally substituted non-aromatic heterocyclic ring;

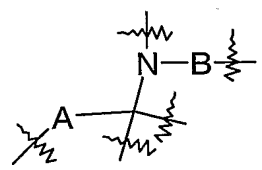
**A** is selected from:

- (i) a direct bond;
- (ii) optionally-substituted C<sub>1-5</sub>alkylene wherein the optional substituents are independently selected from: optionally-substituted C<sub>1-6</sub>alkyl optionally-substituted aryl or optionally substituted arylC<sub>1-6</sub>alkyl;
- (iii) a carbocyclic ring of 3-7 atoms;

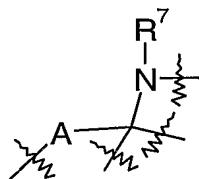
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- (iv) a carbonyl group or  $-C(O)-C(R^d R^d)-$ , wherein  $R^d$  is independently selected from hydrogen and  $C_{1-2}$ alkyl;

or when  $R^3$  is a group of Formula (IIa) or (IIb), the group  forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

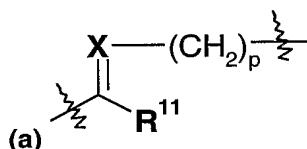
- 5 or when  $R^3$  is a group of Formula (IIa), (IIb), (IIc) or (IId), the group



forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

**B** is selected from:

- (i) a direct bond;  
10 (ii) a group of Formula (IV)



Formula (IV)

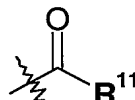
wherein:

- X** is selected from N, CH or a saturated heterocyclic ring,  
15 wherein at position (a) Formula (IV) is attached to the nitrogen atom and the  $(CH_2)_p$  group is attached to  $R^8$ ; and

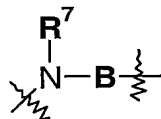
- (iii) a group independently selected from: optionally substituted  $C_{1-6}$ alkylene, optionally substituted  $C_{3-7}$ cycloalkyl, optionally substituted  $C_{3-6}$ alkenylene, optionally substituted  $C_{3-6}$ alkynyl,  $C_{1-6}$ alkoxy,  
20  $(C_{1-5}alkyl)_{aa}-S(O_n)-(C_{1-5}alkyl)_{bb}-$ ,  $(C_{1-5}alkyl)_{aa}-O-(C_{1-5}alkyl)_{bb}-$  or  $(C_{1-5}alkyl)_{aa}-N(R^{15})-(C_{1-5}alkyl)_{bb}-$ ,  
wherein  $R^{15}$  and the  $(C_{1-5}alkyl)_{aa}$  or  $(C_{1-5}alkyl)_{bb}$  chain can be joined to form a ring;

or the group  $-B-R^8$  represents a group of Formula (V)

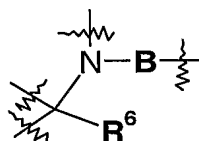
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Formula (V);



or the group together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms;



5 or the group forms a heterocyclic ring containing 3-7 carbon atoms and one or more heteroatoms;

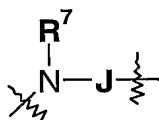
**E** is  $-\text{O}-$ ,  $-\text{S}(\text{O}_n)-$ ,  $-\text{C}(\text{O})-$ ,  $-\text{NR}^{15}-$  or  $-\text{C}(\text{R}^9\text{R}^{10})_q-$ ;

**F** is  $-\text{E}(\text{CH}_2)_r-$  or  $-(\text{CH}_2)_r\text{E}-$ ;

**G** is selected from: hydrogen, halo, CN,  $\text{NO}_2$ , N, O,  $\text{S}(\text{O}_n)$ ,  $\text{C}(\text{O})$ ,  $\text{C}(\text{R}^9\text{R}^{10})_t$ ,

10 optionally substituted  $\text{C}_{2-6}$ alkenylene, optionally substituted  $\text{C}_{2-6}$ alkynylene, optionally substituted heterocyclyl or a direct bond to  $\text{R}^{18}$ ,

**J** is a group of the formula:  $-(\text{CH}_2)_s-\text{L}-(\text{CH}_2)_s-$  wherein when  $s$  is greater than 0, the alkylene group is optionally substituted,



15 or the group together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms;

**K** is selected from: a direct bond,  $-(\text{CH}_2)_{s1}-$ ,  $-(\text{CH}_2)_{s2}-\text{O}-(\text{CH}_2)_{s-}$ ,

$-(\text{CH}_2)_{s1}\text{C}(\text{O})-(\text{CH}_2)_{s2}-$ ,  $-(\text{CH}_2)_{s1}\text{S}(\text{O}_n)-(\text{CH}_2)_{s2}-$ ,  $-(\text{CH}_2)_{s1}\text{N}(\text{R}^{18})-(\text{CH}_2)_{s2}-$ ,

$-(\text{CH}_2)_{s1}\text{C}(\text{O})\text{N}(\text{R}^9)-(\text{CH}_2)_{s2}-$ ,  $-(\text{CH}_2)_{s1}\text{N}(\text{R}^9)\text{C}(\text{O})-(\text{CH}_2)_{s2}-$ ,

$-(\text{CH}_2)_{s1}\text{N}(\text{R}^9)\text{C}(\text{O})\text{N}(\text{R}^9)-(\text{CH}_2)_{s2}-$ ,  $-(\text{CH}_2)_{s1}\text{OC}(\text{O})-(\text{CH}_2)_{s2}-$ ,

20  $-(\text{CH}_2)_{s1}\text{C}(\text{O})\text{O}-(\text{CH}_2)_{s2}-$ ,  $-(\text{CH}_2)_{s1}\text{N}(\text{R}^9)\text{C}(\text{O})\text{O}-(\text{CH}_2)_{s2}-$ ,

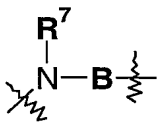
$-(\text{CH}_2)_{s1}\text{OC}(\text{O})\text{N}(\text{R}^9)-(\text{CH}_2)_{s2}-$ ,  $-(\text{CH}_2)_{s1}\text{OS}(\text{O}_n)-(\text{CH}_2)_{s-}$ ,

$-(\text{CH}_2)_{s1}\text{S}(\text{O}_n)-\text{O}-(\text{CH}_2)_{s2}-$ ,  $-(\text{CH}_2)_{s1}\text{S}(\text{O})_2\text{N}(\text{R}^9)-(\text{CH}_2)_{s2}-$ , or

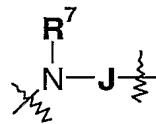
$-(\text{CH}_2)_{s1}\text{N}(\text{R}^9)\text{S}(\text{O})_2-(\text{CH}_2)_{s2}-$ ; wherein the  $-(\text{CH}_2)_{s1}-$  and  $-(\text{CH}_2)_{s2}-$  groups are independently optionally substituted by hydroxy or  $\text{C}_{1-4}$ alkyl;

25 **L** is selected from optionally substituted aryl or optionally substituted heterocyclyl;

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- m** is an integer from 0 to 4;  
**n** is an integer from 0 to 2;  
**p** is an integer from 0 to 4;  
**q** is an integer from 0 to 4;  
 5 **r** is an integer from 0 to 4;  
**s** is an integer from 0 to 4;  
**s1** and **s2** are independently selected from an integer from 0 to 4, and  
**s1+s2** is less than or equal to 4; and  
**t** is an integer from 0 to 4;  
 10 **aa** and **bb** are independently selected from 0 or 1  
**cc** is an integer between 0 to 2;  
 with the proviso that
- (i) when **G** is hydrogen, halo, CN or NO<sub>2</sub> then **R**<sup>17</sup> and **R**<sup>18</sup> are both absent;
  - (ii) when **G** is O, S(O<sub>n</sub>), C(O) or C(**R**<sup>11</sup>**R**<sup>12</sup>)<sub>t</sub> then **G** is substituted by a single group  
 15 independently selected from the definition of **R**<sup>17</sup> or **R**<sup>18</sup> and when **G** is a direct  
 bond to **R**<sup>18</sup> then **G** is substituted by a single group selected from **R**<sup>18</sup>; and
  - (iii) when **R**<sup>3</sup> is a group of Formula (IIb), **B** is a group of Formula (IV), **R**<sup>8</sup> is selected  
 from group (i) or (ii) above, **R**<sup>11</sup> is a group of the formula N(**R**<sup>10</sup>**R**<sup>11</sup>) and **R**<sup>1</sup>, **R**<sup>2</sup>  
 and **R**<sup>5</sup> are as defined above then **R**<sup>4</sup> cannot be hydrogen;  
 20 or a salt, pro-drug or solvate thereof.
2. A compound according to Claim 1 wherein **R**<sup>1</sup> is hydrogen.
  3. A compound according to Claim 1 or Claim 2 wherein **R**<sup>3</sup> is selected from a group of  
 25 Formula (IIa) or Formula (IIb).
  4. A compound according to Claim 3 wherein **B** is optionally substituted C<sub>1-6</sub>alkylene or
- the group 
 forms an optionally substituted C<sub>5-7</sub>heterocyclic ring.
- 30 5. A compound according to Claim 1 or Claim 2 wherein **R**<sup>3</sup> is selected from a group of  
 Formula (IIc) or Formula (IId).

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6. A compound according to Claim 5 wherein the group together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms

- 5 7. A compound according to Claim 6 wherein **K** is selected from:  $-(CH_2)_s-$ ,  $-(CH_2)_s-O-(CH_2)_s-$ ,  $-(CH_2)_s-C(O)-(CH_2)_s-$ ,  $-(CH_2)_s-N(R^{18})-(CH_2)_s-$ ,  $-(CH_2)_s-C(O)N(R^{18})-(CH_2)_s-$ ,  $-(CH_2)_s-N(R^{18})C(O)-(CH_2)_s-$ ,  $-(CH_2)_s-S(O)_2N(R^{18})-(CH_2)_s-$ , or  $-(CH_2)_s-NHS(O)_2-(CH_2)_s-$ .

- 10 8. A compound according to any one of Claims 3, 4, 5, 6 or 7 wherein **R**<sup>8</sup> is selected from

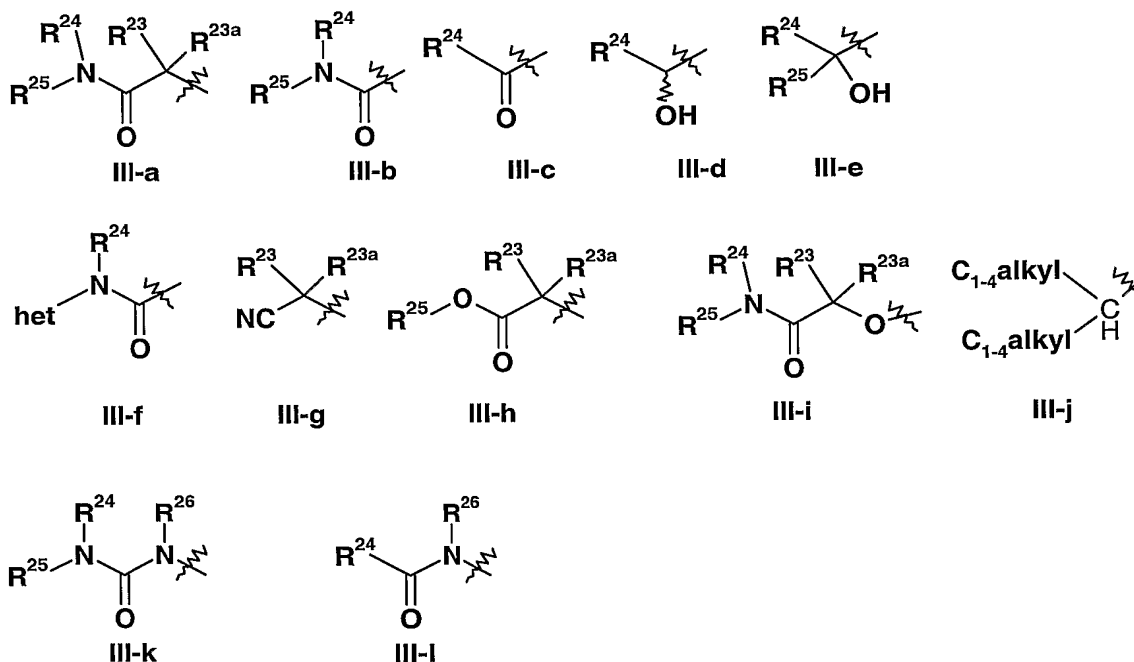
- (i) hydrogen,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl, halo $C_{1-6}$ alkyl, hydroxy, cyano,  $C_{1-6}$ alkyl $S(O)_n-$ ,  $-O-R^b$ ,  $C_{1-4}$ alkoxy $C_{1-4}$ alkyl,  $-C(O)-R^b$ ,  $C(O)O-R^b$ ,  $-NH-C(O)-R^b$ ,  $N,N$ -di- $C_{1-4}$ alkylamino,  $-S(O)_nNR^bR^c$

- 15 where **R**<sup>b</sup> and **R**<sup>c</sup> are independently selected from hydrogen and  $C_{1-6}$ alkyl, and **n** is 0, 1 or 2;

- (ii)  $-(Q)$ -aryl;  
 (iii)  $C_{4-7}$ heterocyclyl, or  
 (iv)  $C_{3-7}$ carbocyclyl;

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9. A compound according to any one of the preceding claims wherein  $R^5$  is a group of Formula (III) wherein the group of Formula (III) is selected from one of **III-a** to **III-l**;



wherein:

- 5      **het** represents an optionally substituted 3- to 8- membered heterocyclic ring containing from 1 to 4 heteroatoms independently selected from O, N and S;
- $R^{23}$  and  $R^{23a}$  are independently selected from hydrogen, fluoro or optionally substituted  $C_{1-8}$ alkyl; or  $R^{23}$  and  $R^{23a}$  together with the carbon to which they are attached form an optionally substituted 3 to 7-membered cycloalkyl ring
- 10       $R^{24}$  is selected from hydrogen, optionally substituted  $C_{1-8}$ alkyl, optionally substituted aryl,  $-R^d$ -Ar, where  $R^d$  represents  $C_{1-8}$ alkylene and Ar represents optionally substituted aryl, and optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 3 further heteroatoms independently selected from O, N and S;
- 15       $R^{25}$  is selected from hydrogen; optionally substituted  $C_{1-8}$ alkyl and optionally substituted aryl;
- or where the group of Formula (III) represents a group of Formula **III-a** , **III-b** or **III-i**, then the group  $NR^{24}(-R^{25})$  represents an optionally substituted 3- to 8-membered heterocyclic ring optionally containing from 1 to 3 further
- 20      heteroatoms independently selected from O, N and S;

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or where the group of Formula (III) represents structure **III-e**,  $R^{24}$  and  $R^{25}$  together with the carbon to which they are attached represents an optionally substituted 3- to 8- membered heterocyclic ring optionally containing from 1 to 4 heteroatoms independently selected from O, N and S;

5  $R^{26}$  is selected from hydrogen or  $C_{1-4}$ alkyl.

10. A compound according to any one of the preceding claims wherein  $R^2$  is selected from an optionally substituted monocyclic aromatic ring structure wherein the optional substituents are selected from cyano,  $NR^eR^f$ , optionally substituted  $C_{1-8}$ alkyl, optionally substituted  $C_{1-8}$ alkoxy or halo wherein  $R^e$  and  $R^f$  are independently selected from hydrogen,  $C_{1-6}$ alkyl or aryl.

11. A compound selected from:

15 2-[2-(1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl)]-4-[1-oxo-2-methyl-2-{4-(1,1-dioxidotetrahydro-3-thienyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;

2-[2-(1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl)]-4-[2-{4-(pyrrolidin-1-ylcarbonylmethyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;

20 2-[2-(1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl)]-4-[2-{4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-6-ylmethyl)piperazin-1-yl}ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;

2-[2-(1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl)]-4-[2-(4-{3-hydroxypyrrolidin-1-ylcarbonyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;

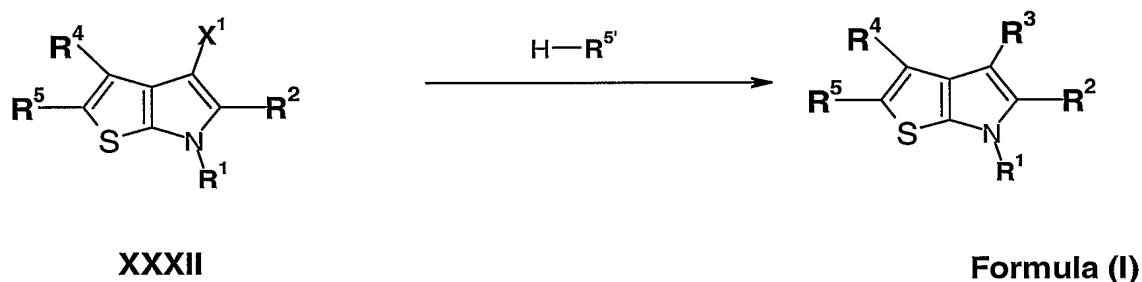
25 2-[2-(1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl)]-4-[2-(4-{3-oxo-3-pyrrolidin-1-ylprop-2-yl}piperazin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole; and

2-[2-(1,1-Dimethyl-2-oxo-2-azabicyclo[2.2.1]heptan-7-ylethyl)]-4-[2-(4-{morpholinocarbonyl}piperidin-1-yl)ethyl]-5-(3,5-dimethylphenyl)-6*H*-thieno[2,3-*b*]pyrrole;

or a salt, pro-drug or solvate thereof.

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12. A compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 11 for use as a medicament.
13. A pharmaceutical formulation comprising a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 11 and a pharmaceutically acceptable diluent or carrier.
14. Use of a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 11, in the manufacture of a medicament for administration to a patient, for therapeutically treating and/or preventing a sex hormone related condition in the patient.
15. A process of producing a compound, or salt, pro-drug or solvate thereof, according to any one of Claims 1 to 11, wherein the process comprises a reaction step selected from any one of (a) to (i):-
- (a) Reaction of a compound of formula **XXXII** with a compound of formula  $\text{H-R}^{5'}$  to form a compound of Formula (I),



wherein  $\text{X}^1$  is selected from:

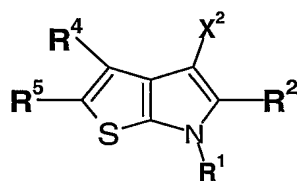
;  $\text{L}^1$  is a displaceable group; and

$\text{H-R}^{5'}$  is selected from:

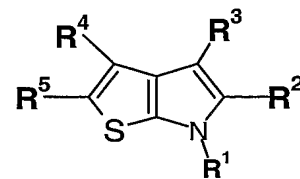
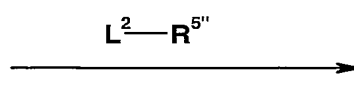
- (b) Reaction of a compound of formula **XXXIII** with a compound of formula  $\text{L}^2\text{-R}^{5''}$  to form a compound of Formula (I),



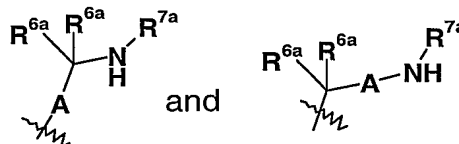
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XXXIII



Formula (I)



wherein  $X^2$  is selected from:

from the definition of  $R^7$  or  $R^{22}$  above, and

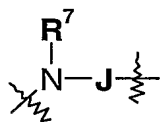
5  $L^2-R^{5''}$  is selected from:  $L^2-B-R^8$ ,  $L^2-J-K-R^8$  and  $L^2-R^{21}$ ;

(c) For compounds of Formula (I) wherein  $R^3$  is a group of Formula (IIa), (IIb), (IIc) or (IId) and  $R^7$  is other than part of a heterocyclic ring or hydrogen, reaction of a compound of Formula (I) wherein  $R^3$  is a group of Formula (IIa), (IIb), (IIc) or (IId) and  $R^7$  is hydrogen with a group of formula  $L^3-R^{7a}$ , wherein  $R^{7a}$  is as defined above for  $R^7$  with the exclusion of hydrogen and  $L^3$  is a displaceable group;

(d) For compounds of Formula (I) wherein  $R^3$  is a group of Formula (IIe) or (IIf) and  $R^{21}$  is other than hydrogen, reaction of a compound of Formula (I) wherein  $R^3$  is a group of Formula (IIe) or (IIf) and  $R^{21}$  is hydrogen with a group of formula  $L^4-R^{21a}$ , wherein  $R^{21a}$  is as defined above for  $R^{21}$  with the exclusion of hydrogen and  $L^4$  is a displaceable group;

(e) For compounds of Formula (I) wherein  $R^3$  is a group of Formula (IIe) or (IIf) and  $R^{22}$  is other than hydrogen, reaction of a compound of Formula (I) wherein  $R^3$  is a group of Formula (IIe) or (IIf) and  $R^{22}$  is hydrogen with a group of formula  $L^5-R^{22a}$ , wherein  $R^{22a}$  is as defined above for  $R^{22}$  with the exclusion of hydrogen and  $L^5$  is a displaceable group;

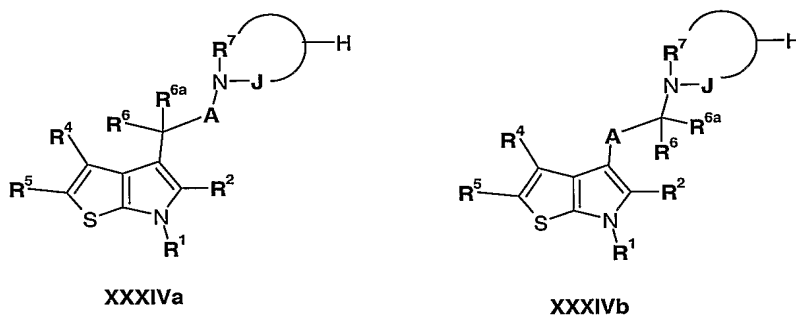
(f) For compounds of Formula (I) wherein  $R^3$  is a group of Formula (IIc) or (IId) and



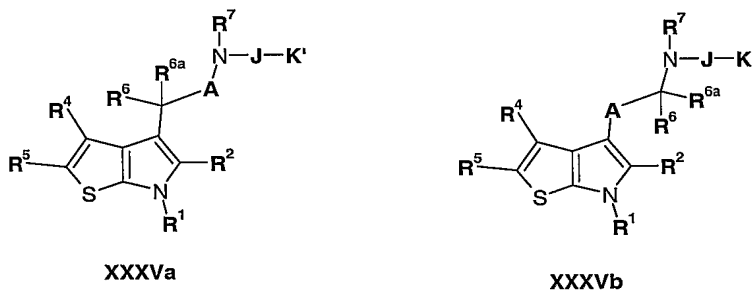
the group together forms an optionally substituted heterocyclic ring containing 4-7 carbons atoms, reaction of a compound of Formula XXXIVa or

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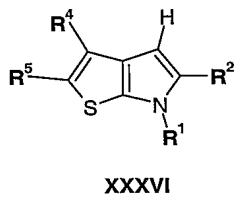
XXXIVb, with a compound of Formula  $L^6-K-R^8$ , wherein  $L^6$  is a displaceable group



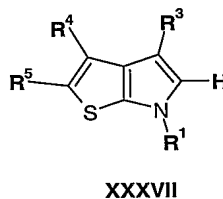
(g) For compounds of Formula (I) wherein  $R^3$  is a group of Formula (IIc) or (IId),  
 5 reaction of a compound of Formula XXXVa or XXXVb, with a compound of Formula  $L^7-K''-R^8$ , wherein  $L^7$  is a displaceable group, and wherein the groups  $K'$  and  $K''$  comprise groups which when reacted together form  $K$ ,



(h) reaction of a compound of Formula XXXVI with an electrophilic compound of the  
 10 formula  $L^8-R^5$ , wherein  $L^8$  is a displaceable group



(i) reaction of a compound of Formula XXXVII with a compound of the formula  $L^8-R^5$ ,  
 wherein  $L^8$  is a displaceable group



and thereafter if necessary:

i) converting a compound of the Formula (I) into another compound of the Formula (I);

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- ii) removing any protecting groups;
- iii) forming a salt, pro-drug or solvate.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 03/03631

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D495/04 A61P15/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

PAJ, WPI Data, EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 53602 A (MERCK & CO INC ;WALSH THOMAS F (US); UJJAINWALLA FEROZE (US)) 14 September 2000 (2000-09-14) cited in the application page 3, line 21 -page 3, line 25; claims; examples	1-15
A	WO 02 24703 A (TIMMERS CORNELIS MARIUS ;AKZO NOBEL NV (NL); KARSTENS WILLEM FREDE) 28 March 2002 (2002-03-28) page 1, 1st and 2nd paragraph claims; examples	1-15



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

14 November 2003

Date of mailing of the international search report

25/11/2003

Name and mailing address of the ISA

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Authorized officer

Schmid, A

# INTERNATIONAL SEARCH REPORT

Intern al application No.  
PCT/GB 03/03631

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.: 1-10 (partly), 12-15  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 03 /03631

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-10 (partly),12-15

Present claims 1-10 and 12-15 relate to extremely large number of possible compounds, products and methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds, products and methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds based on the disclosure of the present examples, specifically to compounds according to claim 3 and claim 9 insofar as the disclosed sub-structures (III) comprise a C(O)-N or N-C(O) group which is a characteristic feature of the present examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No  
PCT/GB 03/03631

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 0053602	A	14-09-2000	AU	3868500 A		28-09-2000
			CA	2366615 A1		14-09-2000
			EP	1161431 A1		12-12-2001
			JP	2002539124 T		19-11-2002
			WO	0053602 A1		14-09-2000
<hr/>						
WO 0224703	A	28-03-2002	AU	1392902 A		02-04-2002
			BR	0113987 A		12-08-2003
			CA	2422054 A1		28-03-2002
			CZ	20030828 A3		13-08-2003
			WO	0224703 A1		28-03-2002
			EP	1322651 A1		02-07-2003
			NO	20031314 A		21-03-2003
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